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Emergence of W135 Meningococcal Disease

Report of a WHO Consultation,
Geneva 17-18 September 2001

World Health Organization
Department of Communicable Disease,
Surveillance and Response

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World Health Organization
Communicable Disease Surveillance and Response

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1. EXECUTIVE SUMMARY

Neisseria meningitidis serogroup W135 has been associated with cases of invasive infections, including outbreaks of limited size for at least six decades. However, coinciding with Hajj/Omra pilgrimages of 2000 and 2001, Saudi Arabia reported the biggest ever outbreaks with W135 involvement. Following the outbreaks in Saudi Arabia, cases were reported in several countries around the world, and in most of these cases, an epidemiological association with international travel to Saudi Arabia or close contact with pilgrims could be established.

Out of the total 304 cases reported in Saudi Arabia in January - June 2000, 162 cases were laboratory confirmed, out of which 98 belonged to serogroup W135 and 64 to serogroup A. Between mid-March and July 2000, a total of 90 Hajj-related cases of meningococcal disease were reported by 11 countries around the world. Most of these cases were W135. Once again and coinciding with the 2001 Hajj season, a total of 274 cases were reported in Saudi Arabia, and out of the 168 cases where meningococcal serogroup identification was obtained, 152 of these belonged to W135 and 8 to A serogroups. Six countries around the world have reported a total of 50 Hajj-related cases to WHO. Most of the isolates were confirmed as W135 (W135 2a P1.5, 1.2 (ST-11)).

In recent years W135 strains have been identified in countries belonging to the African meningitis belt as well. More recently, strains belonging to a clone closely related to that associated with the 2000 and 2001 outbreaks of Saudi Arabia have been reported in Algeria, Burkina Faso, Central African Republic and Niger. WHO supported carriage studies in 2000 in Oman and in Morocco to investigate the proportion of pilgrims and their household contacts carrying W135 and the rate of carriage acquisition. Preliminary results show that 2.7% of people studied in Oman carried the strain identical to the one responsible for the above Hajj outbreaks.

With new laboratory techniques becoming more widely available, a proportion of the previously non-groupable strains could be positively identified. This might reveal a higher proportion of serogroup W135 than is currently documented. However, the major burden of disease in Africa is currently associated with the serogroup A pandemics originating in the late 1980s and in early 1990s.

The available scientific evidence indicates that serogroup W135 can be associated with outbreaks of considerable size and that this strain is present in a number of geographic areas. However, the present laboratory-based surveillance information is inadequate and there is an urgent need to fully identify and document the prevalence of different meningococcal strains both during epidemics and the inter-epidemic periods in as many areas of the African meningitis belt as possible. The potentially changing epidemiology of the disease is a prerequisite for taking any decision to reorient the current global policy for preventing and/or controlling epidemic meningococcal disease.

There are two specific priority situations that the participants at the meeting discussed. One concerns the protection of travellers Saudi Arabia during Hajj and Ramadan Omra pilgrimages. The other concerns the population of the African meningitis belt countries where epidemic meningococcal disease remains a priority public health concern.

With regard to the protection of travellers to Saudi Arabia during Hajj and Ramadan Omra:

1. Vaccination

The participants endorsed the current requirement of Saudi Arabia for the use of tetravalent meningococcal vaccine (A,C,Y,W135) for all pilgrims at least 10 days prior to arrival in Saudi Arabia.

To that effect, and taking into consideration the availability of tetravalent vaccine and price per dose, WHO is requested to investigate options with the manufacturers to address the supply situation and report to the concerned networks on a continuous basis.

2. Chemoprophylaxis

Participants were concerned about the current provision of ciprofloxacin to all pilgrims from Africa and Indian sub-continent countries upon arrival to Saudi Arabia. Concern was also shown regarding the practice by some countries of providing chemoprophylaxis for returning Hajjis as well.

The usefulness of mass chemoprophylaxis from a public health perspective should be considered. Moreover, attention should be paid to the potential for developing antimicrobial resistance, not only in meningococci but also in other respiratory tract pathogens, i.e. pneumococci, *Haemophilus*, staphylococci, etc., as a result of mass chemoprophylaxis. It is also possible that the clearance of carriage of non-pathogenic strains of *Neisseria* could facilitate subsequent replacement with more virulent organisms.

The group recommended that the studies planned in Saudi Arabia to examine the development of antimicrobial resistance associated with the provision of ciprofloxacin to pilgrims be implemented.

The group suggested that decisions on providing chemoprophylaxis to returning Hajjis be based on a risk assessment for secondary transmission of infection once the pilgrim had returned home and the programmatic feasibility of such actions.

3. Surveillance

The timely sharing of information of disease trends during the Hajj was considered necessary to guide the public health response for returning Hajjis and their families. The group encouraged efforts to enhance global laboratory-based surveillance of meningococcal disease in returning pilgrims.

Strategies to control epidemics in the African meningitis belt

Currently there is not sufficient scientific evidence to indicate that serogroup W135 has displaced serogroups A or C as the major antigenic variants for epidemics occurring in the

meningitis belt countries. Therefore, the meeting made no recommendation to change the current policy for prevention or control of epidemic meningococcal disease at this time.

However, the possibility of such displacement exists and therefore there is an urgent need to obtain the critical evidence essential to inform any decision regarding changes to vaccination policy in the future. Information about the serogroups of meningococci causing outbreaks and about the proportions of the various serogroups causing endemic disease in these countries need to be collected comprehensively as soon as possible.

The group considered that 3 different monitoring studies should be carried out:

1. Monitoring prevalent strains associated with epidemics

a) Longitudinal monitoring studies: Evaluating which serogroups are causing epidemic meningococcal disease in a district throughout the duration of the outbreak. Such activities should be done in at least four countries¹.

b) Cross-sectional monitoring studies: Using 1 to 10 isolates from outbreaks from any district in any country of the African meningitis belt where the epidemic threshold has been crossed, a valuable snapshot of the strains across a wide geographical area would be provided.

2. Monitoring of strains causing endemic disease

It would be desirable to have laboratory confirmation of all clinical cases wherever they occur. The infrastructures need to be developed to ensure diagnosis of cases of meningococcal disease and laboratory identification of causative agents on a continuous basis. The existing initiatives to establish functional central public health laboratories with particular emphasis on bacterial meningitis should be rigorously implemented.

The activities outlined above will provide a fully comprehensive picture of pathogenic strains circulating in the meningitis belt and serve as background for any decision taken to reorient strategies for prevention of epidemic meningococcal disease, including the use of conjugate vaccines for Africa now under development.

The group recommended the development of a specific action plan by 10 October 2001 to address the above issues including the three study approaches. The project will have an operational focal point in WHO Regional Office for Africa (AFRO). Requirements for production and distribution of transport media, and communication between countries and WHO reference laboratories (See Item 10).

¹ Tentatively selected: Burkina Faso, Mali, Niger and Sudan

2. INTRODUCTION

Opening by Dr Guénaél Rodier

The strategy of WHO Headquarters Department of Communicable Diseases Surveillance and Response (CSR) has a threefold approach to dealing with health threats posed by epidemic prone infectious agents. On the one hand, it approaches well known and anticipated epidemic risks through established strategies and programmes for disease prevention and control. On the other hand it deals with unexpected risks with high epidemic potential through a global alert and response system supported by a partnership network all over the globe. Finally, CSR strengthens national capacities of Member States to identify and implement the infrastructure and systems for tackling epidemic prone diseases.

Meningococcal disease provides an illustrative example of these strategies. The countries of the African meningitis belt face an anticipated risk of epidemic disease for which CSR has responded by providing a home for the International Coordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG). At the same time WHO works with its partners on ways to identify and respond to the potential emergence of new epidemic strains. These actions can only succeed if national health systems have the infrastructure and staff to ensure an efficient laboratory-based surveillance to guide the appropriate response.

There has been recent evidence of *N.m.* W135 emerging as a potential public health problem. At this meeting WHO and its partners will consider the current evidence and its implications for any reorientation in the current policy for prevention and control of epidemic meningococcal disease. Where this evidence is currently insufficient the meeting will identify what actions are needed to obtain the required evidence.

The outcome of this meeting will guide the future direction of work carried out through the network of the ICG and also the recently established Meningitis Vaccine Programme. These outcomes will also have an impact on the work carried out by others, among which, the health staff preventing or controlling epidemics at country level remain the most important. WHO will ensure that the recommendations of the participants at this meeting are followed up appropriately.

Introduction and objectives by Brian Greenwood

An outbreak of meningococcal disease that originated in Saudi Arabia during the Hajj in mid-March 2000 spread internationally. A total of 304 cases were reported with more than 50% being laboratory confirmed as W135 and a smaller proportion as serogroup A. In the following months, eleven Member States reported cases due to *N.m.* W135 and in the majority of these cases a link with travel or contact with travellers to Saudi Arabia could be established.

During the Hajj season of 2001, an outbreak of 274 cases of meningococcal disease was reported in Saudi Arabia with a considerable proportion of cases due to W135 serogroup. Other countries that have reported cases due to W135 include Burkina Faso (4), Central African Republic (3), Denmark (2), Norway (4), Singapore (4) and Great Britain (41). The

majority of these cases were associated with international travel of contact with travellers to Saudi Arabia.

The fact that pilgrims returning back from the 2000 or 2001 Hajj seasons developed meningococcal disease due to serogroup W135 does not imply that this serogroup was not circulating before 2000. However, these Hajj-related outbreaks are the largest W135 associated outbreaks ever reported and raise the possibility of W135 serogroup becoming a major public health problem at national or international levels. It is crucial to evaluate the risk of W135 causing major outbreaks. It is also crucial to discuss options for prevention and control that could be made available to those countries where these epidemics could have greatest public health consequences.

The first record of W135 in the African region goes back to 1981-82 in Niger and some years later in The Gambia. The isolates obtained in Niger are probably no longer available but it can be assumed that is not the case for those from The Gambia. These last isolates are very similar to the Hajj isolates and so it is possible that this meningococcus went from West Africa to Saudi Arabia in the late 1990s, although spread in the opposite direction cannot be excluded. Other countries (e.g. Ghana and Mali) had major outbreaks of meningococcal disease in the 90s due to serogroup A, with no evidence of W135 circulating. However, the fact that at the end of the 2001 epidemic in Niger, a high proportion of meningococcal disease cases laboratory confirmed were found to be due to W135 raises concern. There is a need to be sure that the failure to identify W135 during epidemics is not due to weakness of the surveillance system, especially laboratory services rather than a true absence of the serogroup.

The objectives of this meeting are:

- To review the global epidemiological situation of meningococcal disease.
- To review factors associated with differing virulence of meningococcal strains and laboratory methods for identification and characterisation of *N.m.*
- To assess whether the change in meningococcal disease epidemiology is due to a molecular biological event (such as capsular switching) or due to vaccination pressure related to increased use of the meningococcal A-C vaccine in recent years.
- To discuss the implications for the protection policy for Hajj and Ramadan Omra pilgrims and for populations at particularly increased risk of epidemics, i.e. those in the African meningitis belt.

3. ENDEMIC/EPIDEMIC PATTERNS OF MENINGOCOCCAL DISEASE

General background to global epidemiology of meningococcal disease by Nancy Rosenstein

Neisseria meningitidis serogroup A is responsible for the largest proportion of cases of epidemic meningococcal disease occurring globally, with the large majority of these cases occurring in the countries of the African meningitis belt. However, in other parts of the world different serogroups are associated with disease. In the countries of the European region serogroups C and B predominate and this is also true in the American region. Other serogroups such as Y or W135 can cause outbreaks; however these are usually of limited

size. Up until now therefore the global public health importance attached to these serogroups is less than that afforded to serogroup A.

The epidemiology of the disease is dynamic; from the reported information, two broad patterns can be described. The first in areas with low endemicity, where in addition to sporadic cases unpredictable and infrequent outbreaks of limited size occur. The second pattern is observed in hyperendemic countries, e.g. those of the African meningitis belt, where in addition to yearly increases in incidence during the dry season, large epidemics are observed cyclically every 8-12 years.

In most of the countries the control strategies are outbreak-led, and these may include mass vaccination with polysaccharide vaccine once the epidemic has been confirmed. The vaccine used by most countries is the A&C bivalent polysaccharide vaccine. However, the tetravalent A, C, Y, W135 polysaccharide vaccine is used in some countries as well (e.g. USA).

Preventive strategies include vaccination of selected population groups or individuals where the risk of contracting the disease is considered important. For example, military population, selected cohorts of university students, Hajj and Omra pilgrims, or travellers to the African meningitis belt countries during the epidemic season.

Preventive strategies involving routine vaccination are being implemented in some countries. For example routine immunization to the entire population is offered in Saudi Arabia. Other countries vaccinate one third of their schooling populations following a 3-year cycle (e.g. Sudan). Again, up until now countries have used the bivalent A, C polysaccharide vaccine for these routine vaccinations.

A conjugate serogroup C vaccine has been successfully introduced in some European countries. The conjugate vaccine against serogroup A, that could induce long term immunity and prevent disease, is not yet available. Therefore the current reactive strategy for control of epidemic meningococcal disease with polysaccharide vaccine is followed by most countries. However, and in spite of the efforts made, countries have found it difficult to reach vaccination targets. For example, in Ghana only 23% of the target population were vaccinated during the epidemic intervention of 1997. International networks, such as the International Co-ordinating Group on Vaccine Provision for Epidemic Meningitis Control (ICG) have assisted countries to deal with epidemics since 1997 and have strengthened the management capacity of national teams.

The goal is eventually to have a vaccine that can prevent disease. The United Kingdom has introduced the serogroup C conjugate vaccine into routine programmes and it is expected that other countries where serogroup C disease is a major problem will follow this lead.

Current methods of *N. meningitidis* strain characterisation by Dominique Caugant

The dynamics of meningococcal disease remain complex and highly setting-dependent. One aspect of the epidemiology of this pathogen is that carriage of an epidemigenic strain is not automatically manifested as meningococcal disease. Progress on epidemic prediction is slow. Although notification-based surveillance allows the classification of geographic areas by their endemicity level, laboratory-based surveillance is critical to monitor the emergence of *N.m.* pathogenic strains across the world.

Traditionally, antigenic structures have been used to distinguish between meningococcal strains. Serogroup determination based on the capsular polysaccharide is essential because the results will dictate the strategies for disease control that can be used. The classes 1 through 3 outer membrane proteins are porins, which have been used for typing. Variation in the class 1 has been and still is the object of much interest, because of the potential role of the molecule as a vaccine component.

Much information about the population genetics of *N. meningitidis* and the epidemiology of meningococcal disease in the past 15 years has been gained through clonal analyses. Two methods have been employed: multilocus enzyme electrophoresis (MLEE), applied since 1984 to over 10 000 of strains from patients and healthy carriers in all continents and multilocus sequence typing (MLST), a recently developed adaptation of MLEE. The main advantages of MLST are that the alleles are identified directly by their nucleotide sequence, there is more variation at the DNA level (for some genes more than 100 distinct alleles have already been identified), the data are unambiguous and can be compared between laboratories. A central database has been set up, to be used through the Internet.

Among the hundreds of multilocus genotypes identified in meningococci, a dozen of clone-complexes are causing most of the disease in the world and among serogroup B and C organisms, the 4 most important nowadays are the ET-5 complex, the ET-37 complex, Cluster A4 and lineage III. These clone-complexes have been causing epidemic or hyperendemic disease for many years in industrialized countries. In Africa, serogroup A of subgroup III have been the major cause of outbreaks and epidemics since their introduction into the continent after the Hajj of 1987.

Current pandemics include those belonging to serogroup A and the III subgroup. An initial pandemic in the 60s-70s was followed by the second pandemic in the 80s-90s. The A-III pandemic is associated with shorter inter-epidemic intervals. The third pandemic that originated in the 90s has been associated with epidemics achieving the highest ever number of cases recorded.

The clone associated with Hajj-related outbreaks of meningococcal disease in 2000 and 2001 has been identified as W135: 2a: P1.5,2 – ST-11. This clone is rarely identified in Europe, although similar strains had been identified in various African countries in the 1990s.

Discussion:

There is neither scientific evidence on the global direction of W135 nor of the reasons for its emergence at this point in time. If the W135 strains seen in West Africa in the early 80s are not available anymore it is not possible to confirm whether or not these belong to the epidemic clone as that associated with the Hajj outbreaks of 2000 and 2001.

In relation to the possible causes of W135 emergence, capsular switching or the selection due to immunization pressure remain among the hypothesis to be tested.

MENINGOCOCCAL VIRULENCE by David Stephens

The pathogenesis of meningococcal disease can be described under three inter-related headings: 1) virulence of *Neisseria meningitidis*, 2) human transmission and acquisition, and 3) human susceptibility to disease. *N. meningitidis* is a pathogen exclusively of humans. Genetic recombination and genome plasticity are characteristics of this organism and it is an important example of pathogen emergence and evolution. The recently published meningococcal genomes have opened a new opportunity for understanding meningococcal pathogenesis, but the contribution of other factors such as genetic variation, human genetic polymorphism that influence susceptibility and the role of co-factors also need to be better understood. *N. meningitidis* is unique among the major bacterial agents of meningitis in that it causes epidemic as well as endemic (sporadic) disease.

Meningococci are traditionally classified by serologic typing systems based on differences of capsule (serogroup), major outer membrane porin proteins (serotype), other outer membrane proteins (serosubtype), and lipooligosaccharide (immunotype). The analyses of isolates based on genomic typing such as multilocus enzyme electrophoresis typing (ET) and multilocus sequence typing (MLST) have enhanced our understanding of the dynamics of meningococcal carriage, spread and disease. Most epidemic and endemic cases of meningococcal disease are caused by a limited number of genetically defined encapsulated clonal groups. Examples of invasive clonal groups are the ET-37 complex and the ET-5 complex. Invasive clonal groups can be characterized by high rates of meningococcal disease following nasopharyngeal acquisition, especially when first introduced into a population.

Components associated with the meningococcal outer membrane including pili and other proteins, a short-chained lipopoly(oligo)saccharide, and capsular polysaccharide, are major contributors to the virulence of *N. meningitidis*. The meningococcal genome is ~2,200 kb (~51% G + C), small in comparison to that of *E. coli*, and has numerous repetitive elements and polymorphic regions. Genome sequencing projects of two meningococcal Z2491 (serogroup A) and MC58 (serogroup B) are completed and a third, serogroup C, strain (FAM18) is being sequenced. The meningococcal capsule locus, which has significantly lower than average G + C content, appears to share a common molecular evolutionary origin with the capsule gene loci of other pathogenic type II capsule producers (e.g., *E. coli* K1 and *H. influenzae*), suggesting possible horizontal acquisition of this virulence locus. The outer membrane components of *N. meningitidis* (e.g., pili, LOS, Opa proteins, Opc, capsule) vary in expression or structure at high frequencies (10^{-2} to 10^{-4} /cell/generation). Variation is the result of genetic switches that turn expression of a component on or off, regulate the amount of a component or alter the structure of a component.

Capsule is a major, if not the major, virulence factor. Meningococci isolated from the blood or cerebrospinal fluid of patients with invasive meningococcal disease almost always express capsules of serogroups A, B, C, Y or W-135. Capsules impart antiphagocytic, anti-adherent and antibactericidal properties to the meningococcus. Meningococcal capsular polysaccharides associated with invasive disease contain, except for serogroup A, sialic acid. Capsule production, like many other virulence factors, is phase variable. Types of meningococcal capsule variation include on-off phase variation, regulation of the amount of capsule expressed, and structural transformation resulting in the replacement of a capsular serogroup. Switching of the capsule biosynthesis operon, that is a gene conversion of the capsule polymerase by transformation, can occur *in vivo*. The W-135 *N. meningitidis*

outbreaks associated with the Hajj in 2000 and 2001 are members of the ET-37 complex usually associated with serogroup C. However, very closely related W-135 ET-37 strains have been recovered from patients and carriers for a number of years prior to the Hajj outbreaks. While serogroups A, B and C remain the causes of large epidemic outbreaks, the emergence of Y, W-135, and possibly X indicate the need for continued and enhanced surveillance. The development of new meningococcal vaccines holds great promise for the prevention of diseases due to *N. meningitidis*, but we must continue to dissect the biology of this pathogen.

4. EMERGENCE OF *N. meningitidis* SEROGROUP W135 DISEASE RELATED TO THE HAJJ

Outbreaks in Saudi Arabia in 2000 and 2001 by Nancy Rosenstein

Since early 90s Saudi Arabia has documented cases of meningococcal disease caused by *N.m.* W135. It is unfortunate that no strains are available prior to 2000 and therefore the comparison between the current pathogenic strains and the previous ones is not possible.

Saudi Arabia reported outbreaks of meningococcal disease during Hajj in 2000 and in 2001. Out of 274 cases reported in 2000, 152 were due to W135, and of the 130 reported in 2001, 76 were due to serogroup W135. The majority of the other cases where strains were identified belonged to serogroup A.

Although meningococcal disease due to serogroup A was present, the proportion of cases due to serogroup W135 was unusually high. Epidemiological analysis shows that in both 2000 and 2001, one outbreak due to serogroup A and another due to serogroup W135 were occurring at the same time. For example, during 2000 Hajj season, the outbreak due to serogroup A, with the median on 5 April 2001, would have preceded by one week to the subsequent W135 outbreak.

The case fatality ratio associated with the 2001 outbreak due to *N.m.* W135 was 26%. A high proportion of cases had concurrent chronic illnesses. Fifty-nine per cent of the cases had been previously vaccinated with bivalent polysaccharide vaccine.

Prevention and control strategies in Saudi Arabia by Amin Mishkas

Following an outbreak of meningococcal disease due to serogroup A in 1974, when 2673 cases were reported, Saudi Arabia introduced the vaccination with monovalent A vaccine. After another outbreak in 1986 with 1619 cases reported, 7.5 million people from Saudi Arabia were vaccinated with bivalent A+C meningococcal vaccine. Later in 1992, Saudi Arabia moved to a routine immunization programme for its entire population, whereby one third of the population is vaccinated every year. In 1993 the surveillance system was revised and meningococcal disease was included as a disease for priority notification.

The health authority of Saudi Arabia requests that all pilgrims present a certificate of vaccination with bivalent A+C vaccine against meningococcal disease administered at least 10 days prior to arrival in the country. In addition to this measure, all pilgrims coming from countries belonging to the African meningitis belt countries or the Indian sub-continent are provided with ciprofloxacin (1g single dose) upon arrival in Saudi Arabia.

Pilgrims coming from areas where an outbreak has been reported are provided with ciprofloxacin as well.

In addition to the above measures, pilgrims are advised to wear masks in order to reduce the risk of transmission during Hajj. This measure is not accepted generally, and only some groups, for example pilgrims from Malaysia, follow such advice.

The total official number of pilgrims expected to visit Saudi Arabia for the 2002 Hajj/Omra season is approximately 1.5 million people. To prepare for the 2002 season Saudi Arabia has purchased 1.5 million doses of tetravalent meningococcal vaccine (from GlaxoSmithKline). This vaccine will be administered to all Saudi national pilgrims, to those covered under routine programmes in priority sites (e.g. Mecca, Medina) and that are over 2 years of age², and to high-risk group populations (e.g. military, health staff³). A limited stock of tetravalent meningococcal vaccine will be reserved to vaccinate pilgrims coming from abroad where evidence of vaccination is questioned. In addition, the Health Authority of Saudi Arabia plans to expand targeted routine vaccination to all population as of 2003 and plans to purchase 2.5 million doses of tetravalent meningococcal vaccine for this purpose.

The actual situation in Saudi Arabia merits special attention. Indeed, there are a considerable number of illegal immigrants not reached by the formal health services. These populations do not have access to health care and therefore are not vaccinated. In order to protect these people, vaccination posts are established around the Holy Mosque.

There is a problem of pilgrims arriving in Saudi Arabia with false vaccination certificates as well. The request for vaccination with tetravalent meningococcal vaccine could worsen this situation, not only because the price of the vaccine is considerably higher, but also because the global availability of this vaccine is limited at present.

The Saudi Arabian Health Authorities discuss ways to address the above issues on a bilateral basis with countries of the meningitis belt, and occasionally donate vaccine to countries that cannot afford it. It opens temporary health centres that can vaccinate unimmunized persons that request it. Other ongoing activities concerning the prevention and control of epidemic meningococcal disease include a carriage prevalence study in Mecca and another study on impact of mass chemoprophylaxis with ciprofloxacin.

² Children below 2 years are vaccinated with monovalent A meningococcal vaccine.

³ The Health Authority of Saudi Arabia has been using tetravalent meningococcal vaccine for all health care workers since 1998.

Evidence of international spread of the outbreak in Europe in 2000 by Anne Perrocheau

In France during March 2000 there were cases of meningococcal disease due to serogroup W135 and an epidemiological association with previous travel or contact with travellers to Saudi Arabia could be established. Soon after, on 8 April, all Hajj pilgrims and their household contacts were advised to visit the nearest health centre to take a 2-day rifampicine treatment course. However, in practice this measure was implemented with 2 weeks delay. A retrospective analysis of the impact of the above preventive measures among the general population showed no difference of effect among pilgrims and their contacts. However, these results did not achieve statistical significance.

Following other notifications of W135 in various European countries, an international study was carried out, whereby a total of 90 cases reported in 9 European countries were considered to be associated with recent international travel to Saudi Arabia. Out of these, in 84 cases, W135 was identified and 6 were classified as "probable case" of Hajj associated meningococcal disease. France and Great Britain were the most affected countries with 41 and 18 cases respectively. Epidemic peaks were different when classifying cases as per pilgrims, household contacts, contacts, or when no "contact" relationship could be established. The median age was 51 years for pilgrims and 2 years for non-pilgrim cases. The overall case fatality ratio was 15.6% and, generally speaking, higher than that seen in other epidemic meningococcal disease episodes caused by other serogroups.

Evidence of spread of the outbreak in the United Kingdom in 2000-2001 by Mary Ramsay

In March 2000, the reference laboratory in England noticed an increase in cases of W135 infection, many of which were associated with pilgrims returning from the Hajj. By the end of March 2001, 51 cases of W135 2a P1.5, 1.2 (ST-11) had been identified of which 8 were in pilgrims, 22 in contacts of pilgrims and 21 who had no apparent contact. One additional group A infection had been identified in a pilgrim and 17 cases of W135 infection not further characterized had been confirmed by Polymerase Chain Reaction (PCR).

Transmission was maintained for several months after the Hajj. For Hajj 2001, tetravalent vaccine was recommended but did not become available until January 2001. Therefore, only sufficient doses were sold to vaccinate 47% of the pilgrims. Despite this vaccination, another 38 cases of the outbreak strain were reported this year, including 6 in pilgrims, 17 in contacts and 15 with no history of contact. The attack rates in 2001 were similar to those in 2000 but none of the pilgrims had received tetravalent vaccine and only 1 of the 17 cases had been in contact with a pilgrim who had received tetravalent vaccine.

Analysis of case fatality indicates that the outbreak strain has a higher case fatality ratio than all meningococcal disease, and than W135 strains of other serotypes. This case fatality ratio did not differ from C2a strains, however, suggesting that the strain shares characteristics with other strains from the ET37 complex.

MLST is being used to further define PCR confirmed cases that are caused by the outbreak strain. Surveillance in Europe has indicated that the strain continues to circulate in Germany, France, the Netherlands and the United Kingdom in summer 2001.

Evidence of spread of the outbreak in Oman in 2000 and 2001 and ongoing operational research by Said Al-Lamki

Oman reported 18 cases of meningococcal disease from March to July 2000. The majority of these cases were confirmed as W135 and in all but one the association with previous international travel to Saudi Arabia or close contact with travellers could be established. Thirteen patient samples were analysed at the WHO Collaborating Centre for Meningococci in Oslo, and all samples were confirmed as belonging to the clone associated with the Hajj, that is, W135: 2a:P1.5,2,- ST-11. This strain is rarely found in Oman, where meningococcal disease is unusual and outbreaks rare.

Oman participated in a WHO multi-country study⁴ to estimate the proportion of carriage of *N.m.*W135 among pilgrims and family contacts and the rate of carriage acquisition. This study was carried out in the South Batinah Region of Oman, during October-November 2000.

A total of 399 people (50 pilgrims and 349 of their family contacts) from a total of 46 family groups were selected by cluster sampling from 4 Wilayats (sub-region). Three throat swabs were collected by standard swabbing techniques from individuals and a total of 1157 samples were examined for *N.m.*W135. There were a total of 102 samples positive for *Neisseria* and among them, 18 were *Neisseria meningitidis*. Of these, 11 belonged to the Hajj clone, and 7 belonged to other serogroups.

23.9% of the family groups were found to harbour at least one carrier of *N.m.* W135. Overall carriage prevalence of 3.76% (10% among pilgrims and 2.8% among family contacts) was observed. Prevalence of W135 was significantly higher among the pilgrims. Children under 15 years of age were found to have an increased tendency for acquiring the carrier state. There was no association between the family size or occupation to prevalence of *N.m.* W135 carriage.

From 1 January to 15 September 2001 there were 14 cases of meningococcal disease, of which 9 in children below 10 years of age. Nine out of the 10 cases where strains were characterized were due to *N. meningitidis* W135 and one to serogroup A. Twelve of these cases happened between the second half of March and the end of April. In 9 of these cases an association (Hajjis or their contacts) with travel in Saudi Arabia for Hajj in the previous 2 weeks was established. This association could not be established in the case due to *N.m.* serogroup A.

The policy for prevention and control of epidemic meningococcal disease in Oman relies on surveillance and immediate reporting (mandatory since 1991) and includes a) immediate case management in a hospital setting with chemoprophylaxis and vaccination for close

⁴ WHO supported this study in Morocco and in Sudan as well. The study in Oman was supported directly by the WHO Collaborating Centre for Meningococci in Oslo/Norway; the study in Morocco by the WHO/CC in Marseilles/France; and the study in Sudan by the National Reference Centre for Meningococci of Orebro/Sweden.

contacts; b) mass vaccination in case of outbreaks due to serogroups A or C; and c) preventive vaccination for all Hajj pilgrims at least 10 days prior to departure for Saudi Arabia (since 1988). All these pilgrims will be vaccinated with tetravalent polysaccharide vaccine as of the next Hajj season.

Qatar and Kuwait provide ciprofloxacin to all pilgrims coming back from Hajj; Oman does not yet and only gives chemoprophylaxis to cases and their household contacts.

5. EVIDENCE OF EMERGENCE OF SEROGROUP W135 IN ASSOCIATION WITH EPIDEMICS IN THE AFRICAN MENINGITIS BELT

2001 Data from Burkina Faso and Niger by Jean-Michel Alonso and Isabelle Parent du Châtelet

During a joint mission of the Association pour l'Aide à la Médecine Préventive and the Institut Pasteur, 94 cerebrospinal fluids (CSF) and 4 serum samples from 58 patients in Burkina Faso and from 40 patients in Niger were collected between the 10th and the 30th of June 2001 (weeks 15-26), during a field investigation.

Cerebrospinal fluids and serum samples were tested by PCR for the presence of *Streptococcus pneumoniae* (Sp) DNA, for the presence of *N.m.* DNA as well as for the presence of *Haemophilus influenzae* type b (Hib) DNA. Samples positive for Nm were further tested by PCR for capsule genes to predict the serogroups A, B, C, Y and W135. Among 32 *N.m.* PCR positive samples (55%) from Burkina Faso, 8 corresponded to serogroup A, 12 to serogroup W135 and 2 to serogroup C. PCR failed to predict serogroup in 10 samples. PCR amplification of capsule genes of Nm led to the identification of 16 serogroup A, 12 serogroup W135 and 1 serogroup C among 31 Nm PCR positive samples (78%) from Niger, while 2 failed to determine the serogroup.

Thus, among the *N.m.* positive samples for which serogroup could be predicted, 38 % corresponded to serogroup W135, 38% corresponded to serogroup A, and 5% corresponded to serogroup C. Systematic questionnaires revealed no link to the 2001 Hajj pilgrimage (neither travel nor contact with pilgrims) for the W135 cases.

In addition, 12 strains of *Neisseria meningitidis* (Nm) had been isolated from other CSF samples. Among four strains isolated in Burkina Faso, only one was A: 4: P1,9 while the 3 others were W135:2a: P1.-5,2. Among eight *N.m.* strains from Niger, seven isolates had the antigenic formula A: 4: P1,9 and one was W135:2a:P1-5,2.

The findings of the mission highlight the importance of obtaining more complete information on the serogroups associated with an epidemic event to complement this cross sectional study. Moreover the need for further improvement in the surveillance system is clear. Indeed, the fact that there is nearly no information on the prevalence of different serogroups during inter-epidemic periods, and that the information available during the epidemic periods is deficient, is a matter for concern. In addition to improving the quality of surveillance, the strategy for prevention and/or control also needs to be strengthened.

For example, in Burkina Faso vaccination campaigns started late in every district where the epidemic threshold had been crossed; and there is confusion over the emergency mass vaccination and the application of a policy of cost recovery at community level.

Immediate steps should be taken to investigate the prevalence of pathogenic serogroups, and especially W135, all through the epidemic season. In order for this to happen there is a need for training and diagnostic materials to be established at country level. For example, i) all countries should have latex diagnostic kits available to identify circulating serogroups; ii) all countries should be able to culture strains; and iii) to carry out full molecular typing of strains with the effective network support from WHO Collaborating Centres for Meningococci and other reference laboratories as needed.

Data on serogroups, types and sub-types isolated from Africa by WHO Collaborating Centres and Reference laboratories

a) WHO Collaborating Centre in Marseille, by Pierre Nicolas

Every year the WHO Collaborating Centre in Marseille receives meningococcal strains from Africa. All these strains are characterized by grouping, typing, subtyping and multilocus sequence typing (MLST). MLST allows the Sequence Type (ST) of a strain to be defined and to follow hypervirulent clones all over the world. MLST will replace multilocus enzyme electrophoresis (MLEE) in the future.

Between 1998 and 2001 most of the "African" strains received in the laboratory of Marseille were meningococci serogroup A:4:P1,9 that belonged to subgroup III (defined by MLEE) and characterised either by ST-5 or ST-7 (MLST). ST-5 strains, responsible for a pandemic wave, were introduced in the "meningitis belt" in 1987 and were isolated from most of the cases and outbreaks during the last 10 years. They were isolated from recent outbreaks in Senegal and in Guinea-Bissau as well. ST-7 meningococci, responsible for a new pandemic were isolated in 2000 Chad and 1999 Sudan outbreaks. In Niger ST-5 and ST-7 strains were isolated during the 2000 outbreak.

In 2000, the laboratory began to receive some W135: 2a: P1.2, 5 meningococci. ET-37 complex (MLEE) and ST-11 (MLST). Pulsed Field Gel Electrophoresis allowed differentiating the W135 2000 outbreak that began in Mecca from the W135 ET-37 complex ST-11 strains already identified in Africa.

In 2000 W135 belonging to the "outbreak clone" were isolated in Senegal and in Mauritius; and in 2001 in Senegal, Mauritius and Algeria. These meningococci were responsible for only a few cases. Some W135 meningococci that were different from the outbreak clone were isolated in Cameroon as well.

Surveillance must be improved for assessing the full significance of these observations.

b) WHO Collaborating Centre in Oslo, by Dominique Caugant

Information obtained by the WHO Collaborating Centre in Oslo on strains circulating in Africa are mainly the results of a decade-long collaboration with Epicentre and Médecins sans Frontières. Cerebrospinal fluid samples from patients with suspected meningococcal meningitis are inoculated in Trans-Isolate media produced in Oslo and sent back to the Collaborating Centre for isolation and characterization of the organism. Meningococcal strains are serogrouped and serotyped using monoclonal antibodies and assigned to a clone using multilocus enzyme electrophoresis and/or multilocus sequence typing. The antibiotic

susceptibility pattern of the strains is tested by the Etest method. When cultivation is negative, the samples are analysed by the polymerase chain reaction (PCR).

Results from 1998-2001 were presented. Most strains recovered from outbreaks and epidemics were serogroup A and belonged to subgroup III. However, a few serogroup B (from Algeria only), C and W135 strains were also identified. While all 23 samples from Angola, Burkina Faso, Central African Republic, Ethiopia and Niger in 2000 harboured serogroup A strains of subgroup III, 9 of the 13 samples from Burkina Faso in 2001 were serogroup W135. One W135 strain was also found in Congo, but this strain was not related to the clone causing the epidemic after the Hajj 2000.

Analysis of the carrier strains recovered in Oman in 2000 showed that 11 of the 18 meningococcal strains belonged to the clone causing the epidemic after the Hajj 2000.

This clone might originally have been endemic in Africa; the most closely related strains were recovered from Mali and Algeria in the mid-1990s. The strains of the Hajj 2000 W135 clone are not particular in their antibiotic susceptibility pattern.

6. POSSIBLE STRATEGIES TO BE ADOPTED TO PROTECT HAJJIS AND THEIR CLOSE CONTACTS, RECOMMENDATIONS

Current practice:

The Health Authority of Saudi Arabia publishes and disseminates as widely as possible the health measures required for all Hajjis visiting the country during Hajj and Omra periods. These include:

a) Vaccination: The current control strategy is the vaccination against the disease with tetravalent meningococcal vaccine at least 10 days prior to arriving in Saudi Arabia. All pilgrims must present a certificate of such a vaccination.

The above raises some concern for two reasons. The first reason is the price of the tetravalent vaccine. With a per-dose price varying from US\$5.6 for Saudi Arabia, or US\$20.0 for United Kingdom, to US\$50.0 for USA, the price remains a significant barrier to many countries. This is especially so for countries in the African meningitis belt and when compared to the per-dose price of the bivalent A+C meningococcal vaccine, of US\$0.20.

The second reason for concern is the global availability of this product. There are two manufacturers (e.g. Aventis and GlaxoSmithKline) of the tetravalent meningococcal vaccine that have their entire production purchased in advance. In one instance it only manufactures this vaccine for the market in the USA, and in the other case production has reached the full capacity of existing facilities and all this production is earmarked already.

The two observations above are well known to the Health Authority of Saudi Arabia, and as a temporary measure, they could restrict the requirement for tetravalent vaccination to only Hajj pilgrims for the next season. Due to the global limitations in tetravalent vaccine supply, Ramadan Omra pilgrims could exceptionally be accepted if presenting a certificate of vaccination with bivalent A+C meningococcal vaccine.

In the present situation, WHO is requested to continue negotiations with the manufacturers with a view to implementing solutions to the supply problems as soon as possible. Quality control of vaccination certificates needs to be addressed as well and reinforcement of this measure by all parties.

b) Chemoprophylaxis: Any pilgrim arriving in Saudi Arabia without a valid certificate of vaccination with tetravalent meningococcal vaccine administered at least 10 days prior to arrival will be provided with 1g of ciprofloxacin. Pilgrims coming from countries belonging to the African meningitis belt or to the Indian subcontinent; or from areas with ongoing outbreaks will be provided with chemoprophylaxis as well. In this regard Saudi Arabia has ordered 1 million doses of ciprofloxacin.

Some countries (e.g. Gulf countries) provide chemoprophylaxis to pilgrims returning to their countries of origin. Saudi Arabia advises these countries to include the contacts of pilgrims as well in the chemoprophylaxis programme.

The above two measures are implemented under the assumption that chemoprophylaxis ought to provide community protection by eliminating carriage. In this regard it was remarked that people who received chemoprophylaxis could become re-colonized a few days after finishing their treatment course. In addition, large scale chemoprophylaxis with ciprofloxacin could induce resistance in *Neisseria meningitidis* or pneumococcus and this resistance is likely to be induced at a quicker rate than with other antimicrobials (e.g. rifampicine).

The United Kingdom had considered administering ciprofloxacin to returning pilgrims and their contacts in 2000. However, after careful consideration of the risk of adverse events and the practical difficulties to ensure the supervision of chemoprophylaxis to these returning pilgrims and their contacts, the initiative was abandoned.

The group agreed that administering chemoprophylaxis to returning pilgrims should be based on the risk of secondary transmission of infection for contacts. For example in the USA the carriage rates for W135 was found to be low among pilgrims and no cases of W135 were reported in 2001 Hajj season, indicating that routine chemoprophylaxis for this group at least would not have been beneficial.

c) Surveillance: Any strategy for prevention or control of epidemic meningococcal disease needs to focus on the prevailing dynamics of pathogenic strains. Therefore, there is a need to monitor endemic as well as epidemic meningococcal disease. It was felt necessary to share information between countries on any outbreak, and especially at present on serogroup W135 disease.

Saudi Arabia plans to carry out carriage studies among pilgrims attending Hajj.

Group conclusions:

The outbreaks of meningococcal disease reported in Saudi Arabia during Hajj and Ramadan Omra seasons of 2000 and 2001 and their international spread constitute the biggest ever reported outbreak of *N.m.* W135.

There is not enough scientific evidence to form a judgement on the probability of W135 displacing other pathogenic serogroups and therefore its potential as a public health hazard cannot be ascertained at present. With a view to gaining the required evidence, outbreak strains as well as endemic strains need to be monitored and followed up regularly. Thus, the most urgent action at this moment is to strengthen laboratory-based surveillance at country level.

With recent improvements in laboratory techniques there is the possibility of identifying more W135 among the strains classified until now as "non-groupable". As a result, there could be a higher proportion of meningococcal disease due to W135 than is currently recognized.

The population at risk should be protected with the most appropriate vaccine available. In special high-risk situations, as for example, the Hajj pilgrimage, the Health Authority of Saudi Arabia has moved to requiring vaccination with tetravalent meningococcal vaccine for all pilgrims and for the attending health staff. This measure is endorsed fully by this meeting of experts. The group requests that WHO negotiates with the manufacturers and partners on options to increase access to the tetravalent vaccine at a fair price.

Concerning the practice of mass chemoprophylaxis as a preventive measure the group is concerned, not only as regards the usefulness of this measure from a public health perspective, but also as regards the potential long-term antimicrobial resistance that can be induced.

Group Recommendations with regard to the protection of travellers to the Kingdom of Saudi Arabia during Hajj and Ramadan Omra (see in General Recommendations)

7. IMPLICATIONS OF CURRENT EVIDENCE FOR STRATEGIES TO CONTROL EPIDEMICS IN THE MENINGITIS BELT. RECOMMENDATIONS FOR STRATEGY AND FOR OPERATIONAL RESEARCH

Current available evidence

There is evidence of W135 circulating in Africa since the early 1980s. Unfortunately, there are no strains available from that time to investigate if these belong to identical epidemic clones. Identical strains to those identified during the outbreaks reported in Saudi Arabia in 2000 and in 2001, W135: 2a:P1.5,2, have been identified in Algeria, Burkina Faso, Democratic Republic of Congo, Niger, and Senegal in 2001. In Niger, out of 519 samples from cases in 2001 where the strain was fully identified, 2.7% were W135.

In April 2001 a team collected samples at the end of the epidemic period in Burkina Faso (35) and in Niger (40), and found a considerable proportion of W135 (37%), A (39%) and C (7%) serogroups, with the rest not being typable. The study has limitations due to the small size of the convenience sample collected at the end of the epidemic and with the available information it is not possible to draw conclusions concerning the role of serogroup W135 in association with epidemics.

If capsular switching is resulting in epidemic W135 disease it can be hypothesized that comensal W135 organisms escape capsular antibodies induced by bivalent A & C vaccination and that epidemic C2a, P1-2.5 switches capsule gene to become W135 2a P1-2.5.

At the same time there may be an artificial masking of the W135. Since the epidemic response includes mass vaccination with bivalent A+C meningococcal vaccine, it could well be the case that other serogroups are present, however, as these are not looked for actively and they are not detected. In Niger, out of 193 isolates characterized, 156 were serogroup A and 14 were W135. However, since all these samples belong to the end of the epidemic curve, it is not possible to be sure that W135 present earlier in the outbreak was picked up by the laboratory.

Another situation that needs to be analysed is the impact that mass vaccination has on the prevalent pathogenic strains. For example, after the mass vaccination in Ghana in the 90s with bivalent A+C vaccine, the proportion of serogroup X increased considerably.

WHO Collaborating Centres already provide laboratory support to countries of the meningitis belt but there is a need to reinforce this work. For example, the WHO Collaborating Centre in Oslo provides trans-isolate media⁵ to all countries requesting it. However, less than 10% come back to Oslo for full strain characterization (e.g. an average of 50 samples from 1995-99, and around 150 in 2000). The WHO Collaborating Centre in Atlanta or in Marseilles face similar situations. At the same time, it is only through the collaboration with these WHO Collaborating Centres that the global picture concerning meningococcus will be determined. Thanks to their research we know that although in some countries (e.g. Mali and Algeria of mid-90s or Taiwan in 2000) the W135 serogroup was present, these strains belong to different clone to that associated with Hajj outbreaks of 2000 and 2001.

Overall serogroup A disease predominates in African countries. However, it is critical that laboratory surveillance is improved within national networks where meningococcal disease occurs and that international networks support national work.

Discussions on the implications of current evidence for prevention and control strategies and for additional measures and research

There is now evidence that *N. meningitidis* W135 is involved in meningococcal disease outbreaks in several countries; however, the available evidence to support a change in strategy for epidemic control of meningococcal disease (e.g. use of tetravalent meningococcal vaccine in place of the bivalent vaccine) requires additional research studies and the following specific questions need to be addressed:

- What serogroups and genotypes are involved in meningococcal disease outbreaks in the countries of the African meningitis belt?
- What serogroups and genotypes are involved in endemic disease in these countries?

⁵ Trans-isolate media developed first by Ajello, GW (1984)

It is only after accurate information on the above questions is analysed that it will be possible to determine the most appropriate composition for both the polysaccharide vaccine and the future conjugate vaccine for Africa.

To answer these questions three different types of study are needed. Firstly, longitudinal studies documenting the organisms involved throughout the course of an epidemic and covering at least one district are carried out in 3-4 countries in the African meningitis belt. These studies could be implemented in countries with a reasonably performant surveillance system; where clinical specimens are routinely collected; and if at all possible, where a network of laboratory services is available with a national laboratory acting as reference centre for the above network.

Secondly, ad-hoc studies to fully identify strains involved at the start of any outbreak in any district where epidemic meningococcal disease occurs. This project could provide a better picture of circulating pathogenic strains in various countries and identify the emergence of any particular clone.

Thirdly, long-term studies to investigate and support laboratory-based surveillance of endemic disease that would need to be implemented on a continuous basis.

The support for carrying out the above studies could be translated into logistic support (e.g. from local and/or international nongovernmental organizations), material (e.g. Trans-isolate media or reagents that the WHO Collaborating Centres could provide), or technical assistance (e.g. training of national responsible staff and/or external technical support when needed). There are a number of practical issues that will require resolution at the national level with the support of international partners once the studies are launched. These operational research studies should be coordinated with other ongoing activities from WHO or other partners, such as the Paediatric Bacterial Meningitis Network and the Laboratory Strengthening team based at the WHO/CSR Office in Lyon, France.

8. IMPLICATIONS FOR SUPPLY AND COST OF ANY RECOMMENDATION TO USE TETRAVALENT (A,C,Y, W135) MENINGOCOCCAL POLYSACCHARIDE VACCINE

The group discussed the recommendation to be given to countries in the hypothetical situation whereby the first laboratory confirmation of samples of meningococcal disease indicated serogroup W135 disease. The current practice requires that prior to launching a mass vaccination campaign with the bivalent meningococcal vaccine, serogroups A or C be confirmed in a number of epidemic cases at the beginning of an epidemic season. Logically, in the case of a significant (relevant) proportion of these first cases being identified as serogroup W135, mass vaccination with tetravalent meningococcal vaccine should be recommended. However, this recommendation may not be feasible in the near future, given the limited availability of this vaccine and the access that countries in the African meningitis belt have to this product.

The group proposed that in the absence of the appropriate vaccine for launching the mass vaccination campaigns, efforts should be focused on case management. Another option would be chemoprophylaxis for exposed household contacts. Both alternatives should be

considered in the light of the political or public health perspective. At global level, however, the group strongly recommended the constitution of a contingency stock of tetravalent meningococcal vaccine that could be sent immediately when needed. There will be a need to define the amount of this stock and identify the resources needed for this purpose. The International Coordinating Group (ICG) on Vaccine Provision for Epidemic Meningitis Control mechanism was suggested among the possible options.

9. OVERALL RECOMMENDATIONS

Recommendations of the meeting with regard to the protection of travellers to the Kingdom of Saudi Arabia during Hajj and Ramadan Omra:

1. Vaccination: The participants to the meeting endorse the current requirement of Saudi Arabia for the use of tetravalent vaccine for all pilgrims at least 10 days prior to arrival in Saudi Arabia.

To that effect, and taking into consideration the availability of tetravalent vaccine and price per dose, the WHO is requested to investigate options with the manufacturers to address the supply situation and report to the concerned networks on a continuous basis. Present estimated requirements are 1.5 million doses for pilgrims travelling in the coming Hajj season in 2002. These additional doses would cover the pilgrims from countries other than Saudi Arabia, who have already purchased vaccine to cover their own needs.

2. Chemoprophylaxis: The current practice of providing ciprofloxacin to all pilgrims coming from African and Indian sub-continent countries upon arrival to Saudi Arabia raises concern among the participants to the meeting. This concern relates to the potential for the development of resistance to quinolones in pathogenic organisms. There is also a theoretical possibility that clearance of non-pathogenic strains of *Neisseria* could facilitate replacement with more virulent organisms. The group recommended that the studies planned in Saudi Arabia on the development of antimicrobial resistance should be implemented.

The group discussed the current practice by some countries of providing with chemoprophylaxis for returning Hajjis. The decision to implement such policy should depend upon the programmatic feasibility and the assessment of risk for secondary disease.

3. Surveillance: The timely sharing of information of disease trends during Hajj was considered necessary to guide public health response to returning Hajjis and their families. The group encourages efforts to enhance the global surveillance of meningococcal disease in returning pilgrims.

Conclusions and recommendations of the meeting on the implications of current evidence for strategies to be used in controlling epidemics in the meningitis belt countries and for additional measures and research

In order to obtain the critical evidence essential to inform any decision about changing vaccination policy, two questions must be answered. The first is about the serogroups of meningococci that are causing outbreaks in the African meningitis belt countries. The

second concerns the proportion of various serogroups that are causing endemic disease in this region.

With a view to answer the first question, the meeting agreed that two types of investigations should be carried out.

1. Ad-hoc studies documenting outbreaks. In addition to the above, isolates should be obtained and fully identified from every district in which the epidemic threshold has been crossed in all countries. Efforts should be made to involve an increasing number of countries in this practice.

2. Longitudinal studies evaluating serogroups causing epidemic meningococcal disease in a district throughout the duration of the outbreak are needed, since some recent evidence suggests that more than one serogroup may be involved in a single outbreak. Such studies should be done in at least 4 countries (Burkina Faso, Mali, Niger and Sudan).

3. Long-term studies documenting endemic disease. An answer to the second question requires development of infrastructure for continuous laboratory identification of etiological diagnosis for cases of bacterial meningitis. This will provide a picture of circulating pathogenic strains and will serve as background for any decision to re-orient the strategies for prevention of epidemic meningococcal disease and use of vaccine now under development.

WHO/AFRO's Hib Pediatric Bacterial Meningitidis Surveillance Network could help to accomplish the above. However, the group also recommended urgent development of a specific action plan for implementation of the three types of studies outlined. A first draft should be shared with meeting participants by September 24th, with comments due by October 1. A final version will be prepared by October 10. The plan must include a budget and timeline for specific milestones. The project will have an operational focal point in WHO/AFRO. Specific attention must be paid to requirements for production and distribution of transport media, and communication between countries and WHO reference laboratories (See item 10: Proposed Plan of Action).

Concerning the options available in cases where the laboratory confirmed samples as W135, or any other antigenic variant at the beginning of the epidemic season in an area, the group agreed that careful analysis of each case would be mandatory. There would be no use in providing general recommendations in the present situation of limited tetravalent meningococcal vaccine availability. However, what is certainly needed is an accurate and urgent confirmation of outbreaks prior to vaccination and an improved laboratory-based surveillance.

10. PROPOSED PLAN OF ACTION

Enhancing Meningococcal Surveillance for African “Meningitis Belt” Countries

04 October 2001

I. Background

Historically, epidemics of meningococcal disease in the meningitis belt of sub-Saharan Africa have been primarily due to *Neisseria meningitidis* serogroup A strains and, less often, serogroup C strains. In 1987, an epidemic of serogroup A meningococcal disease occurred associated with the annual Hajj pilgrimage in Saudi Arabia. At least 1841 cases were reported during 1987 in Saudi Arabia as well as many Hajj-associated cases internationally¹. The following year, the same clone of serogroup A caused large epidemics in African meningitis belt countries with more than 70 000 cases² and attack rates as high as 1%.³

Serogroups other than A and C, such as B, X, Y and W135 cause sporadic meningococcal disease worldwide, but have not been implicated as the cause of large epidemics. In spring 2000, an epidemic caused concurrently by serogroups A and W135 *N. meningitidis* strains occurred in Saudi Arabia associated with the Hajj. A total of 264 suspected cases and 70 deaths were reported in this epidemic, resulting in an overall attack rate of 15 cases/100 000 Hajj pilgrims. Out of the 161 confirmed cases for which identification of *N. meningitidis* serogroup was available, 93 cases (53%) were caused by *N. meningitidis* serogroup W135. In addition, at least 99 cases of serogroup W135 meningococcal disease among Hajj participants occurred in countries outside of Saudi Arabia, including countries in the African meningitis belt. Serogroup A cases preceded the median onset of disease in serogroup W135 cases by 2 weeks.⁴ This prompted speculation about the possibility of capsular switching from A to W135 capsule as one possible explanation of this unusual epidemic.

Past surveillance data has documented the presence of *N. meningitidis* serogroup W135 in Saudi Arabia as early as 1990 and in Africa (Senegal and Niger) as early as 1981.⁵ When these strains were compared to serogroup W135 strains from Saudi Arabia in 2000, the same clone was found to be circulating globally as long as 30 years ago.^{6,7} This

¹ Moore PS, Reeves MW, Schwartz B, Gellin BG, Broome CV. Intercontinental Spread of an Epidemic Group A *Neisseria Meningitidis* Strain. *Lancet*. July 29 1989.

² WHO Report on Global Surveillance of Epidemic-prone Infectious Diseases, World Health Organization, 2001, WHO/CDS/CSR/ISR/2000.I.

³ Control of Epidemic Meningococcal Disease, WHO practical guidelines (2nd Edition), World Health Organization, 1998, WHO/EMC/BAC/98.3

⁴ Lingappa J, Al-Rabeah A, Hajjeh R, Mustaffa T, Fatani A, Al-Bassam T, Badrkhan A, Turkistani A, Al-Hamdan, Al-Jefferi M, Rosenstein N. Epidemic Serogroup W-135 Meningococcal Disease Associated with the 2000 Hajj Pilgrimage. Manuscript in preparation.

⁵ Kwara A, Adegbola A, Corrah PT, Weber M, Achtman M, Morelli G, Caugant D.A., Greenwood B.M. Meningitis caused by serogroup W135 clone of the ET-37 complex of *Neisseria meningitidis* in West Africa. *Tropical Medicine and International Health* 1998; 3 (9):742-746.

^{6,7} Popovic T, Sacchi CT, Reeves MW, Whitney A.M., Mayer L.W., Noble C.A., Ajello G.W., Mostashari F., Bendana N., Lingappa J., and Rosenstein N.E. *Neisseria meningitidis* serogroup W135

suggested that recent capsular switching from A to W135 was an unlikely cause for the concurrent epidemics in Saudi Arabia during the 1999-2000 season. In 2001, 130 meningococcal cases were recorded in Saudi Arabia; of the 81 for which serogroup was obtained, 76 (94%) were serogroup W135. In the 13 African meningitis belt countries, more than 50 000 suspected cases and 4,000 deaths were reported in 2000-2001, with country attack rates more than 100 times that of the serogroup W135 epidemic in Saudi Arabia. Although these epidemics were considered to be caused by serogroup A *N. meningitidis*, serogroup W135 strains were isolated from cases in Burkina Faso and Niger.^{8,9} Of 58 cerebrospinal fluid (CSF) and 4 serum samples from Burkina Faso and Niger tested positive for the presence of meningococcal DNA by polymerase chain reaction (PCR), 37% were identified as serogroup W135.⁹ These isolates and specimens were primarily collected from at the end of the epidemics in these countries. None of the patients reported travel to the Hajj or contact with pilgrims. Although the clone identified was related to the W135 clone identified at the Hajj in 2000, molecular subtyping showed slight differences between the strains pattern.

Current efforts to control meningococcal disease epidemics in Africa generally rely upon early recognition of surveillance-based epidemic threshold rates to prompt mass vaccination campaigns with the bivalent meningococcal A/C polysaccharide vaccine. A quadravalent meningococcal A/C/Y/W135 polysaccharide vaccine is licensed but not used in Africa because the quantities are limited, it is a more expensive vaccine, and with the formerly typical patterns of serogroup-specific disease, protection afforded by the W135 component of the vaccine provided marginal benefit. The recent change in Saudi Arabia's vaccination requirements from bivalent to quadravalent vaccine for travel to the Hajj will further decrease the potential quantities of quadravalent vaccine available for control of epidemics in Africa. Improving access to the quadravalent vaccine will require evidence of strain distribution and the magnitude of strain burden.

As outlined at the Meeting on the Emergence of W135 Meningococcal disease in Geneva on 17-18 September 2001, to obtain the critical evidence essential to inform any decision about vaccination policy, surveillance for the strains causing meningococcal epidemics in Africa is a priority for the 2001-2002 season. Early detection of an epidemic caused by serogroup W135 *N. meningitidis* would require rapid changes in control strategies. Longitudinal surveillance is needed because the data from Saudi Arabia suggests that in some settings, meningococcal epidemics caused by more than one serogroup can overlap. Further information should also be gathered on the serogroups causing endemic disease in Africa to better understand circulating strains. In addition, this information will be helpful to understand circulating pathogenic strains as well as to ensure that new serogroup-specific conjugate vaccines are optimally formulated to control first epidemics and then endemic disease in meningitis belt countries.

isolates from U.S. travellers returning from Hajj are associated with the ET-37 complex. *Emerg Infect Dis* 2000; 6:10-11.

Mayer L.M., Reeves M.W., Al-Hamdan N., Sacchi C.T., Taha M.-K., Ajello G.W., Schmink S.E., Noble C.A., Tondella M.L.C., Whitney A.M., Al-Mazrou Y., Al-Jefri M., Mishkhis A., Sabban S., Caugant D., Lingappa J., Rosenstein N.E., and Popovic T. The 2000 outbreak of W135 meningococcal disease: not emergence of a new W135 strain, but clonal expansion within the ET-37 complex. (Submitted for publication).

^{8,9} CDC. Unpublished data.

Association pour l'Aide à la Médecine Préventive (AMP), Institut Pasteur. Manuscript in preparation.

II. Aims/Objectives

1) Epidemic Meningitis Surveillance. To determine the role of *N. meningitidis* serogroup W135 in the occurrence of outbreaks of meningococcal disease in the African meningitis belt to provide new data to assist Member States in evaluating epidemic control strategies. This data will be gathered using 2 complementary strategies:

1A. Enhanced Epidemic Meningitis Surveillance. The proportion of each *N. meningitidis* serogroup causing meningococcal epidemics in 2001-2002 across the meningitis belt will be estimated using a sampling framework focused on early cases. Information on early cases will also assist Member States in decision-making regarding vaccination campaigns.

1B. Comprehensive Epidemic Meningitis Surveillance. The proportion of each *N. meningitidis* serogroup causing meningococcal epidemics in 2001-2002 in one district in 4 selected meningitis belt countries will be evaluated using longitudinal surveillance for the duration of the epidemic. Comprehensive surveillance will provide important information during 2001-2002 and will also provide a framework and serve as a pilot for future enhanced surveillance.

2) Endemic Meningitis Surveillance. The objective of this activity is to characterize the contribution of serogroup W135 disease to endemic meningococcal disease in the meningitis belt. Phase one (2001-02) focuses on development of one sentinel site in the capital city of each country. Phase two (2002-03) focuses on the expansion of this activity to additional sites within each country.

III. Methods

1A. Enhanced Epidemic Meningitis Surveillance.

1A.i. Design. Surveillance will focus on strengthening existing capacity for laboratory-confirmation of meningococcal disease epidemics. AFP-supported personnel will be used to help conduct and supervise enhanced Epidemic Meningitis Surveillance. AFP-supported persons include approximately 10 Ministry of Health provincial active surveillance persons with vehicles, per diem, and fuel money and a WHO EPI focal point in every country. The provincial active surveillance persons visit nearly all districts each month and most major health facilities every 1-2 months. Starting in November-December 2001, the AFP surveillance persons will ensure that all districts in the meningitis belt countries (except Ethiopia and Nigeria) keep an epidemic curve by week of meningitis cases with the alert threshold drawn in at 5 cases per 100,000 population per week. In provinces likely to have an epidemic, the provincial active surveillance person will store Trans-Isolate (T-I) bottles and CSF spinal tap kits HOW MANY? 10?. When each district crosses the meningitis epidemic threshold, the provincial active surveillance person will ensure that CSF samples be collected early in each epidemic from patients meeting the clinical case definition for meningitis. Five to 10 CSF samples will be collected using the T-I bottles and CSF spinal tap kits and transported to the National Bacteriology Laboratory. A stock of T-I bottles and CSF spinal tap kits will also be kept at the National Laboratory to resupply the provinces.

In addition to collection of samples, information will be collected for each patient on demographics, clinical signs, risk factors (i.e., recent travel to Hajj) and prior

meningococcal vaccination. This information will be linked to the laboratory sample using an identification number.

1A.ii. Laboratory testing. Ensuring high-quality testing of CSF specimens in the national bacteriology laboratory and a regional reference laboratory is important. An AFRO-sponsored network of national bacteriology laboratories (similar to the polio laboratory network) is being established complete with quality assurance (QA) and quality control (QC). A laboratory accreditation system is an essential part of a laboratory-based meningococcal surveillance system and will set the groundwork for evaluation of new meningococcal conjugate vaccines. Training of laboratory personnel has with one session in June, 2001, and another scheduled for November.

At the National Bacteriology Laboratory, Gram stain, antigen detection using latex tests (including serogroup W-135 is this feasible?), culture and serogrouping will be conducted. Isolates will be then sent to the Regional Reference Laboratory using silica gel packs or other appropriate methodology. At the Regional Reference Laboratory, serogroup will be confirmed and testing conducted for antibiotic resistance. Isolates will then be sent to one of the WHO Collaborating Center laboratories for molecular subtyping. The Regional Reference Laboratory will provide QA/QC of the National Laboratory. The WHO Collaborating Center laboratories will provide QA/QC for the regional reference laboratory.

1A.iii. Data analysis. Data will be coded and entered into an EPI INFO database. Data will be analyzed at country, subregional and regional levels.

1A.iv. Coordination. At the national level, surveillance will be coordinated by the 3-person Integrated Disease Surveillance (IDS) team working with AFP-supported persons. The IDS subregional staff will provide technical assistance to the countries and ensure coordination between countries.

1B. Comprehensive Epidemic Meningitis Surveillance

1B.i. Design. Comprehensive epidemic surveillance will focus on gathering longitudinal data on serogroups causing epidemics in several districts in the meningitis belt. At the Meeting on the Emergence of W135 Meningococcal disease in Geneva on 17-18 September 2001, Burkina Faso, Mali, and Niger were chosen as sites for comprehensive surveillance because of the high likelihood that each of these countries would have a meningitis epidemic this year. While the countries are chosen prospectively, one district for comprehensive surveillance will be chosen within each country only after the number of meningococcal cases surpasses the WHO meningitis epidemic.¹⁰

In these districts, every patient who meets the clinical case definition for meningitis will be eligible for enrollment. Given the typical district size, based on a 1% attack rate, as many as 1000 meningitis cases requiring specimen collection could be expected. Specific sampling methodology will be developed depending on the site selected, but the goal will be to enroll 250 patients over the course of each epidemic.

The Enhance Surveillance Coordinator will store T-I bottles and CSF spinal tap kits at the national level and transport them to the affected epidemic. A CSF sample from each

¹⁰ Weekly World Health Organization Epidemiological Record 2000; No. 75 (38): 310 (22 September).

enrolled patient will be collected. Each specimen will be either split between two T-I bottles or between one T-I bottle and one tube for PCR. T-I bottles and PCR tubes will be transported to the National Bacteriology Laboratory.

In addition to collection of samples, information will be collected for each patient on demographics, clinical signs, risk factors (i.e., recent travel to Hajj) and prior meningococcal vaccination. This information will be linked to the laboratory sample using an identification number.

1B. ii. Laboratory testing. At the National Bacteriology Laboratory, Gram stain, culture and serogrouping antigen detection using latex tests (including serogroup W-135), culture and serogrouping will be conducted using one T-I bottle. Isolates will be then sent to the regional reference laboratory using silica gel packs or other appropriate methodology. At the Regional Reference Laboratory, serogroup will be confirmed and testing conducted for antibiotic resistance. The second T-I bottle or PCR vial will be sent directly to the Regional Reference Laboratory for evaluation. Testing of this second sample will provide additional QA/QC for the National Laboratory. Isolates will then be sent to one of the WHO Collaborating Center laboratories for molecular subtyping. The WHO Collaborating Center laboratories will provide QA/QC for the Regional Reference Laboratory.

1B.iii. Data analysis. Data will be coded and entered into an EPI INFO database. Data will be analyzed at country, subregional and regional levels.

1B.iv. Coordination. To ensure completion of this project in 6 months, a national coordinator will be funded for each of the 4 countries in the comprehensive program. The national coordinator will use local physicians and AFP-supported persons to assist in surveillance and transport of specimens (see 1B.i). The coordinator will work for the 3-person IDS team already on site, and with AFP-supported persons. The IDS subregional staff will provide technical assistance to the countries and ensure coordination between countries. In addition, because of the intensity of this project, a strong external technical partner will be paired with each country.

2. Comprehensive Endemic Meningitis Surveillance

The objective of this activity is to characterize the contribution of serogroup W135 disease to endemic meningococcal disease in the meningitis belt. Phase one (2001-02) focuses on development of one sentinel site in the capital city of each country. Phase two (2002-03) focuses on the expansion of this activity to additional sites within each country.

2A Expansion of the AFRO PBM Surveillance Network to include the evaluation of CSF from adults

At this time, the AFRO Pediatric Bacterial Meningitis (PBM) Surveillance Network (SN) is focused on developing capacity for surveillance for pediatric bacterial meningitis at one site in the capital city of each country. Expansion of activities to include the evaluation of adult CSF could be easily accomplished within this framework. Clinicians attending the adult wards will require orientation and then training for case recognition, criteria for administration of lumbar punctures and handling and transport of CSF. Within the microbiology laboratory it is recommended that all CSF results be recorded in one register following the guidelines of the AFRO PBM SN manual. PBM SN surveillance officers will also need guidance on the reporting of results.

To establish the AFRO PBM Surveillance Network in each country, activities in 2001 are devoted to identifying and developing one sentinel site in every capital city. The largest pediatric ward in the capital city was chosen not only for sentinel surveillance but also to develop national support for this activity.

At each site a pediatrician, data manager, and microbiologist are recruited and trained (surveillance, data management, microbiology) together with MOH surveillance officers and personnel from the national public health laboratory. Each site receives funding for capital and recurrent costs associated with surveillance activities including a computer for recording and reporting data and laboratory reagents for culturing cerebro-spinal fluid (CSF).

Oversight of these activities is provided by an AFRO surveillance officer. This person is responsible for site-level performance evaluations which include clinical and laboratory evaluations as well as completeness and timeliness of reporting. The surveillance officer is also responsible for preparing feedback to the sites and surveillance reports for use by technical agencies. Performance of national level meningitis surveillance is evaluated by MOH surveillance officers and the in-country WHO EPI officer. Site-level funding is dependent upon defined performance criteria.

2B Phase Two: Expanded bacterial meningitis surveillance

After phase one surveillance is performing satisfactorily, phase II will be initiated. Phase II focuses on the expansion to additional sites within each country.

VI. Partners

To maximize the potential of these activities and provide technical guidance and assistance, the following partners are proposed:

1. the Vaccine Preventable Disease and Communicable Disease Departments of WHO/AFRO;
2. the department of Vaccines and Biologicals (HTP/VAB) at WHO/HQ;
3. the Communicable Disease Surveillance and Response Department (CDS/CSR) at WHO/HQ;
4. and the following partners who are currently providing technical guidance and support in the meningitis belt countries:
 - 4.1. US National Centers for Disease Control and Prevention (CDC); Meningitis and Special Pathogens Branch; Atlanta, GA; USA
 - 4.2. National Institute of Public Health; Oslo, Norway
 - 4.3. Institut de Médecine Tropicale du Service de Santé des Armées; Armées-Marseille, France
 - 4.4. Institut Pasteur; Paris, France and the Association pour l'Aide à la Médecine Préventive (AMP) à l' Institut Pasteur, Paris, France

ANNEX 1

Agenda

**EMERGENCE OF W135 MENINGOCOCCAL DISEASE
REPORT OF A WHO CONSULTATION, GENEVA 17-18 SEPTEMBER 2001**

AGENDA

17 September 2001

8:30 Registration

9:00 Opening - Dr Guenael Rodier

09:10 Introduction and Objectives – Dr Brian Greenwood, Chairperson

9:15 Background on endemic/epidemic patterns of meningococcal disease

A. General background to global epidemiology of meningococcal disease

- Presentation by Dr Nancy Rosenstein

B. Overview of molecular/genetic epidemiology of meningococcal strains, and factors influencing virulence

- Presentation by Dr Mark Achtman - current status of techniques of sub-typing strains of *Neisseria meningitidis*, how their application has enlightened us regarding the epidemiology and spread of disease (epidemic) causing strains, and most useful current methods

- Presentation by Dr David Stephens – characteristics of organisms of different strains that contribute to virulence

10:00 Presentations on the emergence of *N. meningitidis* serogroup W135 disease related to the Hajj

Presentations of epidemics in Saudi Arabia

- Dr Nancy Rosenstein on the 2000 epidemic in Saudi Arabia
- Representative from Saudi Arabia on 2001 epidemic and other relevant studies undertaken

- Presentations of evidence for international spread. (case numbers, serogroups, sub-typing, clinical presentation, descriptive epidemiology, evidence for sustained transmission of W135, other relevant studies (carriage studies)

- Dr Anne Perrocheau on the outbreak in Europe 2001
- Dr Mary Ramsay on the outbreak in United Kingdom 2001
- Representative from Oman

11:30 Presentation(s) on the evidence of emergence of serogroup W135 in association with epidemics in the African meningitis belt

- 2001 Data from Burkina Faso and Niger – presented by Dr Jean-Michel Alonso/Dr Isabelle Parent du Châtelet
- Data on serogroups and sub-types isolated from Africa by WHO Collaborating Centres/ Reference laboratories

Dr Dominique Caugant – Oslo

Dr Pierre Nicolas – Marseilles

Dr Nancy Rosenstein/Dr David Stephens - Atlanta

12:30 – 14:00 LUNCH

14:00 Discussion on possible strategies to be adopted to protect Hajis and their close contacts, recommendations.

- Discussion moderated by and introduced by WHO/EMRO representative: describing currently implemented measures and indicating the range of measures that could be considered in the discussion
 - Vaccination
 - Chemoprophylaxis/carriage clearance
 - Surveillance
 - other

SECOND DAY

9:00 Discussions on the implications of current evidence for strategies to be used in controlling epidemics in the meningitis belt, recommendations - for strategy and for additional measures/research.

Discussion moderated by and introduced by WHO/AFRO representative/ Jay Wenger

- Surveillance: what are the key surveillance questions?
Options for answers: Expansion of lab capacity (Paediatric Bacterial Meningitidis Surveillance Network)

Others

Rapid evaluation of epidemic

- Strategy for disease control: implications for emergency mass vaccination, implications for preventive vaccination

12:30 – 14:00 LUNCH

Manufacturers of polysaccharide meningococcal vaccines join the meeting

14:00 Presentation of the recommendations

- Rapporteur to present the recommendations

15:00 Presentation of predicted production and availability of tetravalent vaccine by manufacturers

Aventis

GlaxoSmithKline

16:00 Implications for supply and cost of any recommendations to use tetravalent meningococcal polysaccharide vaccine.

Close of meeting

ANNEX 2

List of Participants

**EMERGENCE OF W135 MENINGOCOCCAL DISEASE
REPORT OF A WHO CONSULTATION, GENEVA 17-18 SEPTEMBER 2001**

LIST OF PARTICIPANTS

NIGER:

Dr Mamoudou Harouna Djingarey, Ministry of Health, BP13378 Niamey, Niger. Tel: +227 723 678, Fax: +227 723 025. Email: pasenig@intnet.ne

OMAN:

Dr Said Al-Lamki, Ministry of Health, Oman

SAUDI ARABIA

Dr Al-Mazrou, Ministry of Health, Saudi Arabia

Dr Amin Meshkas, Ministry of Health, PO Box 26650, Riyadh 11496, Saudi Arabia

WHO COLLABORATING CENTRES

Dr Dominique Caugant, WHO Collaborating Centre for Reference & Research on Meningococci, National Institute of Public Health, PO Box 4404 Nydalen N-0403 Oslo, Norway. Tel: +47 22 0423 11, Fax: +47 22 0425 18. Email: dominique@caugant@folkehelsa.no

Dr Pierre Nicolas, WHO Collaborating Centre, BP46, 13998 Marseille Armees, France. Tel: +334 91 15 0115, Fax: +334 91 59 4477. Email: imtssa.meningo@free.fr

Dr N. Rosenstein, Centers for Disease Control and Prevention (CDC), Meningitis and Special Pathogens Branch, Division of Bacterial and Mycotic Diseases, 1600 Clifton Road N.E. - MS C-09 Atlanta, GA 30333, USA. Tel: +1404 639 3158, Fax: +1404 639 3059. Email: nar5@cdc.gov

TEMPORARY ADVISERS

Dr J.-M. Alonso, Centre National de Référence des Meningocoques, Institut Pasteur, 25-28 rue de Dr Roux, 75724 Paris Cedex 15. Tel: +331 45 68 8330, Fax: +331 40 61 3084. Email: jmalonso@pasteur.fr

Dr Ian Feavers, Department of Bacteriology NIBSC, Blanche Lane South Mimms, Potters Bar, Hertfordshire EN6 3QG, UK. Tel: +441 707 654 753, Fax: +441 707 663 796. Email: ifeavers@nibsc.ac.uk

Dr Dan Granoff, Children`s Hospital Oakland Research Institute, 5700 Martin Luther King Jr Way, Oakland, California 94609-1673, USA. Tel: +1510 450 7640, Fax: +1510 450 7910. Email: dgranoff@chori.org

Dr Brian Greenwood, Department of Infectious and Tropical Diseases, London School of Hygiene, Keppel Street, London WC1E 7HT, UK. Tel: +44207 299 4707, Fax: +44207 299 4720. Email: b.greenwood@lshtm.ac.uk

Dr Isabelle Parent du Chatelet, Centre National de Référence des Meningocoques, Institut Pasteur, 25-28 rue de Dr Roux, 75724 Paris Cedex 15. Tel: +331 53 86 8921, Fax: +331 53 86 8939. Email: iparent@aamp.org

Dr Anne Perrocheau, Institut de Veille Sanitaire, 14 rue du Vol d`Osne, 94 Saint Maurice-cedex. Tel: +331 4179 6731, Fax: +331 41 7968 72. Email: a.perrocheau@invs.sante.fr

Dr Mary Ramsay, CDSC, Immunisation Division Public Health Laboratory Service, 61 Colindale Avenue, London NW9 5EQ, UK. Tel: +44208 200 6868, Fax: +44208 200 7868. Email: mramsay@phls.org.uk

PARTNERS

Mr Marc LaForce, Director WHO Conjugate Vaccine Project/PATH, Email: fmlaforce@aol.com

Dr B. Morinière, IFRC (International Federation of Red Cross and Red Crescent Societies), 17 chemin de Crêts, 1211 Geneva 19. Tel: 730 4340, Fax: 733 0395. Email: morinier@ifrc.org

Dr A. Paganini, UNICEF, Senior Adviser Health Programme Division, Three United Nations Plaza, New York, NY 10017. Tel +1212 824 6338, Fax: +1212 824 6484. Email: apaganini@unicef.org

Dr F. Varaine, Conseiller Technique, Département Techniques Médicale, Medecins sans Frontiers, 8 rue Saint-Sabin, 75755 Paris Cedex 11, France. Tel: +331 4021 2935, Fax: +331 4806 6868. Email: fvaraine@paris.msf.org

MANUFACTURERS OF VACCINE

Dr P. Laturus, Aventis Pasteur, 2 Avenue Pont Pasteur, 69007 Lyon, France. Tel: +334 3737 7075, Fax: +334 3737 7830. Email: patrick.laturus@aventis.com

WHO/REGIONAL OFFICES

Regional Office for the Eastern Mediterranean (EMRO)

Dr Nadia Teleb, World Health Organization, WHO Post Office, Abdul Razzak Al Sanhoury Street, Nasr City, Cairo 11 371 Egypt. Tel: +202 670 2535, Fax: +202 670 2492. Email: telebn@who.sci.eg

Regional Office for Africa (AFRO)

Dr I Sow, World Health Organization, Medical School, C Ward, Parirenyatwa Hospital, Mazoe Street, PO Box BE773, Belvedere, Harare, Zimbabwe. Tel: +263 470 6951, Fax: 263 470 0742. Email: sowi@whoafr.org

WHO/HQ

Mr Paul Acriviadis, Procurement Services (PRS). Tel: +41 22 791 2187, Email: acriviadis@who.int

Dr Teresa Aguado, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 2644, Email: aguadoderosm@who.int

Mrs Martha Anker, Integrated Surveillance & Response (ISR). Tel: +41 22 791 2380, Email: ankerm@who.int

Mr Alejandro Costa, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 4965, Email: costaa@who.int

Dr Steve Edgerton, Integrated Surveillance & Response (ISR). Tel: +41 22 791 2586, Fax: +41 22 791 4198. Email: edgertons@who.int

Dr Max Hardiman, Integrated Surveillance & Response (ISR). Tel: +41 22 791 2572, Fax: +41 22 791 4198. Email: hardimanm@who.int

Dr David Heymann, Executive Director, Communicable Diseases, Tel: +41 22 791 2212, Email: heymannd@who.int

Dr Luis Jodar, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 3744, Email: jodarl@who.int

Dr Julie Milstien, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 3564, Email: milstienj@who.int

Dr Chris Nelson, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 3615, Email: nelsonc@who.int

Mr Augusto Pinto, WHO/LYON, 58 avenue Debourg, 69007 Lyon, France. Tel: +334 7271 6473. Email: pintoa@lyon.who.int

Dr Guénaél Rodier, Director, Department of Communicable Disease Surveillance and Response (CSR). Tel: +41 22 791 2109, Fax: +41 22 791 4198. Email: rodierg@who.int

Dr Maria Santamaria, Integrated Surveillance & Response (ISR). Email: mastamaria@hotmail.com

Dr Daniel Tarantola, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 2779, Email: tarantolad@who.int

Dr Jay Wenger, Health Technology & Pharmaceuticals (HTP). Tel: +41 22 791 4511, Email: wengerj@who.int

ANNEX 3

PRESENTATIONS

ANNEX 3.1

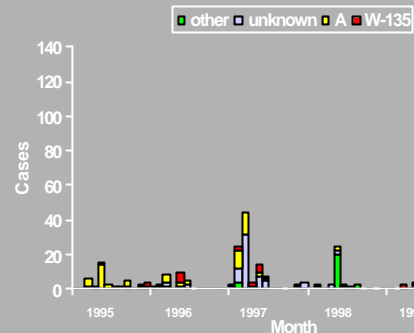
Global epidemiology of meningococcal disease

by Nancy Rosenstein

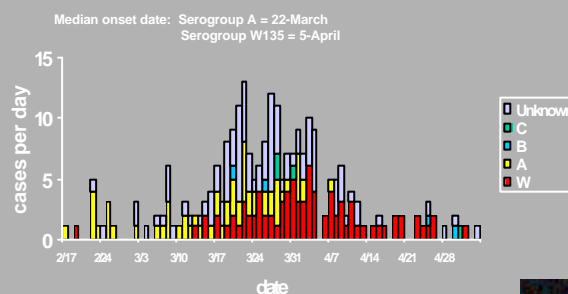
W-135 Meningococcal Disease in Saudi Arabia, 2000

Presented by Nancy Rosenstein, M.D.
Meningitis and Special Pathogens Branch, CDC
September 17, 2001
Geneva

Meningococcal Disease in Saudi Arabia, by month, 1995-2000



Meningococcal Disease in Saudi Arabia, February 17– May, 4 2000



Cases of Meningococcal Disease, Saudi Arabia, 1/24-6/3, 2000

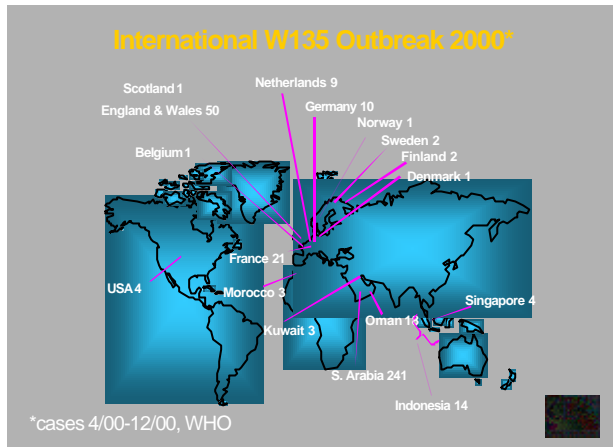
- 264 cases identified in Mecca, Medina and Jeddah
- 253 (96%) laboratory confirmed (culture or latex)
- 161 (64%) serogroup identified
 - 93 (58%) serogroup W-135
 - 60 (37%) serogroup A
 - 4 serogroup B
 - 4 serogroup C

Demographic Characteristics, Meningococcal Cases Saudi Arabia, 2000

Characteristics	Cases (%)
	n=253
Hospital admission (median)	29-March
Female gender	118 (47%)
Age (median) (yrs)	40
Identified in Jeddah	41(16%)
Identified in Mecca	158 (62%)
Identified in Medina	54 (21%)
Chronic illness	44 (17%)
Died	70 (28%)
Prior vaccination	130 (59%)

Attack Rates, Meningococcal Disease, Saudi Arabia, 2000

264 cases
1,733,785 Hajj attendees = 15 cases/100,000



Carriage of *N. meningitidis* among Returning Pilgrims, US, 2001

- Enrolled
 - 452 departing passengers
 - 870 returning passengers (707 pilgrims)
- Returning pilgrims more likely to be carriers than departing pilgrims (2.7% vs. 0.9%, $p=0.09$)
- None of the departing but 6 (0.8%) of returning pilgrims carried serogroup W-135 ($p=0.09$)

Meningococcal Disease, Saudi Arabia, Feb 2 – March 22, 2001*

- 109 cases reported
- 35 deaths (CFR 32%)
- More than half of cases due to serogroup W-135
- Carriage of *N. meningitidis* recorded among returning pilgrims

*personal communication, Dr. El Samani

N. meningitidis Strains from Burkina Faso, 2001

- 4 patients
 - from a single hospital in Ougadougou
 - aged <10 years
- All confirmed to be serogroup W135
- Molecular subtyping
 - PFGE and 16S identical to each other, slightly different from the Hajj-strain but closely related

Issues Regarding Serogroup W-135 Recommendations for Hajj Pilgrims

- Bivalent (A/C) vs quadrivalent (A/C/Y/W135) polysaccharide vaccine
- Economics
- Vaccine supply
- Chemoprophylaxis

Issues Regarding Serogroup W-135 in the African Meningitis Belt

- Serogroup W-135 unlikely to cause epidemics of the same proportion as serogroup A
- Current control efforts should focus on bivalent A/C vaccine after confirmation of serogroup
- Formulation of new conjugate vaccines should focus on early availability of serogroup A

ANNEX 3.2

Current methods of *Neisseria meningitidis* strain Characterization

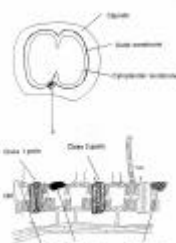
by Dominique Caugant

(WHO Collaborating Centre, Oslo)

Epidemiological forms of meningococcal disease

- Asymptomatic carriage: About 10% of the population; up to 100% in selected groups
- Endemic disease: 1-2 cases of meningitis/septicemia per 100 000; uniformly distributed in time and space
- Hyperendemic disease: Moderate increase in incidence (5-10 cases/100 000) over a long period
- Epidemic disease: Focal outbreaks or countrywide, up to 500/100 000 in some countries
- Pandemic: Epidemic disease involving one or several continents

Main surface structures of *Neisseria meningitidis*



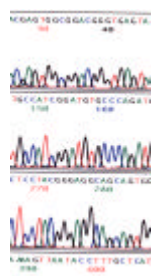
Capsular polysaccharide: Serogroup A, B, C, W, ...

Outer membrane proteins:

- **Class 2/3 (PorB):** Serotype 1, 2a, 2b, 4, 15... (4 variable regions/conformational epitopes)
- **Class 1 (PorA):** Serosubtype P1.1, P1.2... (2 variable regions/linear epitopes)
- **Lipopolysaccharides:** Immunotype L3,7,9...

Antigenic formula: A: 21: P1.20.9: L3,7,9

MLST - Method

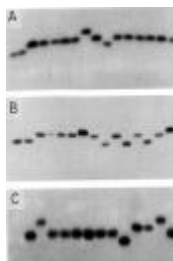


- 7 housekeeping genes spread on the whole chromosome
- Alleles are identified directly by their nucleotide sequence
 - More variation at the DNA level (over 100 alleles)
 - Sequences are accurate
- Fully portable between laboratories
- Central database that can be interrogated electronically via the internet

Clonal analyses

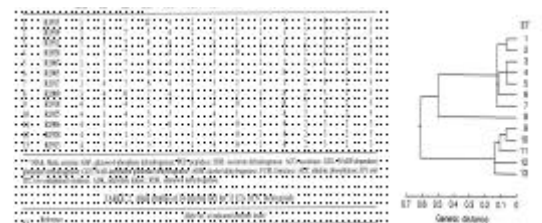
- **Multilocus enzyme electrophoresis (MLEE):**
 - First applied to *N. meningitidis* in 1984
 - More than 10 000 strains from healthy carriers and patients in all continents have been analysed
 - Identified pathogenic genotypes associated with epidemic and hyperendemic disease
- **Multilocus sequence typing (MLST):**
 - Developed in 1998
 - More than 1000 meningococcal strains analysed

MLEE - Method



- 14 randomly selected housekeeping genes spread on the whole chromosome
- Moderate variability (up to 17 alleles at one locus)
- Good reproducibility
- Provides the appropriate degree of variation for global epidemiology
- Inconvenients:
 - Time-consuming, cumbersome
 - Requires reference strains for standardization

MLEE data

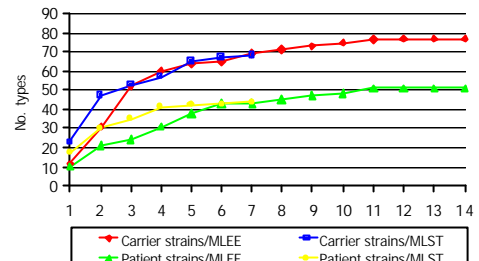


MLST analyses of bacterial isolates

	ABCZ	ADK	AROE	FUM	GDH	PDHC	PGM	ST
N 100	27	6	9	3	5	6	16	NT
N 200	3	6	9	5	9	6	9	41
N 300	4	10	5	4	6	104	8	NT
N 400	6	5	2	12	12	13	14	NT
N 500	2	3	4	3	8	4	6	11
N 600	4	10	5	4	6	3	8	32
N 700	3	6	9	5	9	6	9	41
N 800	12	6	9	9	9	6	9	43
N 900	2	3	4	3	8	4	103	NT
N 1000	9	6	9	9	9	6	17	110

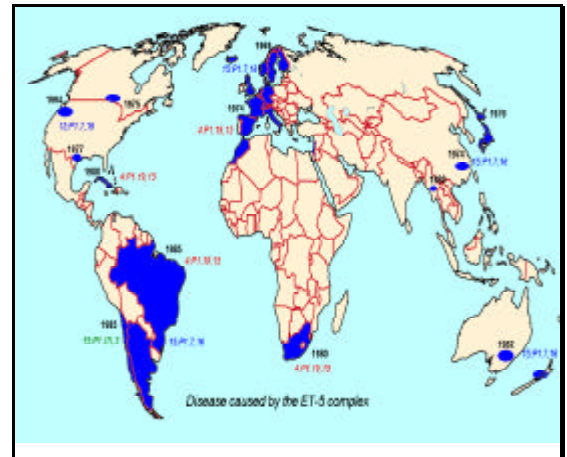
ST = sequence type

Relationship between number of analysed genes and number of distinguished types



Clone-complexes associated with epidemic and hyperendemic disease

Clone-complex	Serogroup	Serotype
ET-5 complex	B, (C)	15:P1.7,16 4:P1.19,15 15:P1.(7),3
Lineage III	B	4:P1.(7),4
ET-37 complex	C, B, (W135, Y)	2a:P1.5,2 2a:P1.5,10
Subgroup III	A	4,21:P1.20,9



Antigenic and genetic variation in the ET-5 complex

- Less than 50% of the ET-5 complex strains in Norway are of the original serotype: serotype 15:P1.16.
- Among 237 patient strains analysed with Mabs in the past 5 years, 26 antigenic combinations were evidenced.
- Sequencing of *porA* revealed an even greater amount of heterogeneity.
- All genes that have been sequenced in strains of the ET-5 complex have shown allelic variation, mainly as a result of recombinational events.
- Escape mechanism to avoid immune pressure?

Bactericidal titers of sera collected after vaccination with the Norwegian group B meningococcal vaccine

Epitope	Sequence	Mean titer Pre-vacc.	Mean titer Post-vacc.	% Responders
P1.16a	PAYYTKDT	1.3	6.0	100
P1.16c	PAY - TKDT	0.2	2.3	79

Characteristics of epidemics caused by the ET-5 complex

- Delay between introduction of the clone and onset of epidemic, as a result from low transmissibility
- Persistence over several decades (hyperendemic waves)
- High incidence among teenagers
- High fatality ratio, as a result from a high proportion of septicemia cases

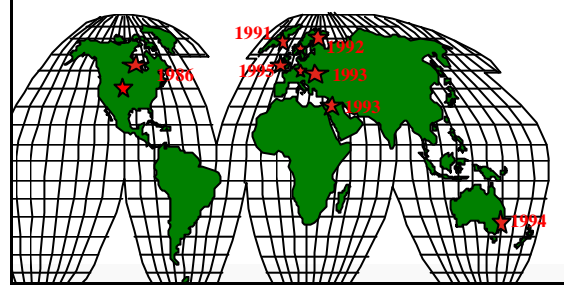
The ET-37 complex

- First identified in USA in 1917
- Relatively homogeneous in serotype:serosubtype
- Associated with the 4 serogroups containing N-acetyl neuraminic acid (B, C, W135 and Y)
- Caused outbreaks/epidemics in:
 - the US Army in the 1960s
 - Brazil in the early 1970s (serogroup C)
 - South Africa in the late 1970s (serogroup B)
 - Europe, USA in the 1980s (serogroup C)
 - Africa (serogroup C, W135 and Y)

ET-15

- A clone of the ET-37 complex characterized by a rare allele at the FUM locus
- First identified in Canada in 1986
- Responsible for most of serogroup C disease in Canada in the 1990s and outbreaks in the United States
- Global spread within a few years

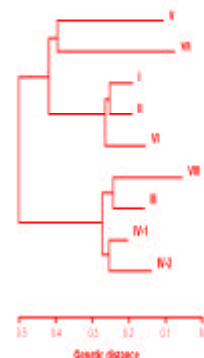
Outbreaks caused by ET-15 isolates

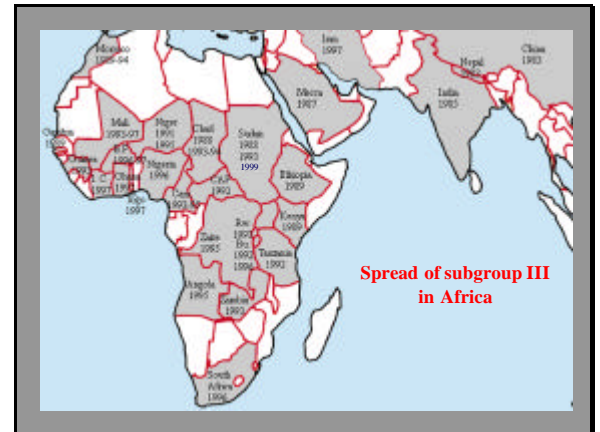
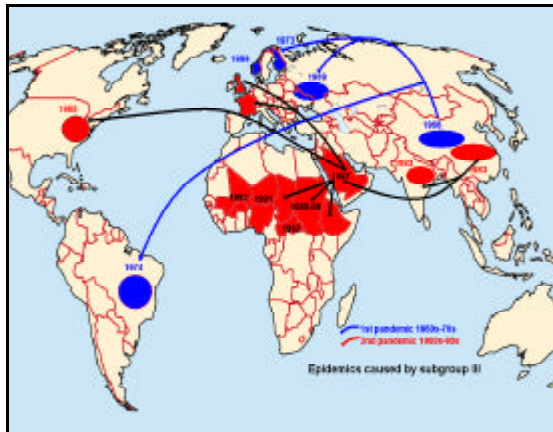


Hajj 2000 W135 clone

- 90 cases in Saudi Arabia
- Increase of W135 disease in France and UK after the hajj 2000
- W135:2a:P1.5,2 - ST-11 - Rare in Europe
- Most closely related to W135 strains previously identified in Africa in the 1990s

Genetic relationships among serogroup A meningococci



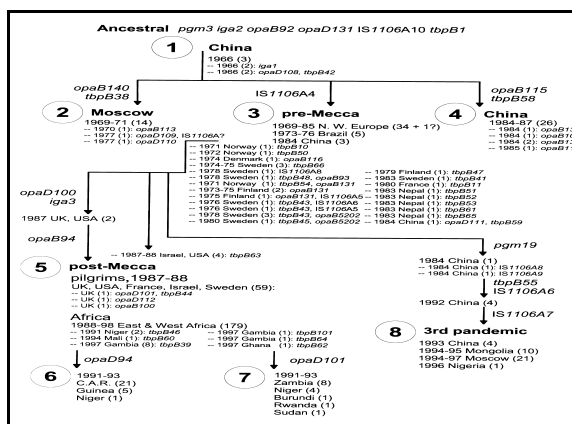


Microevolution of subgroup III

Allele prior to 1987	Allele after 1987	Event
<i>opaD131</i>	<i>opaD100</i>	point mutation
<i>opaB92</i>	<i>opaB94</i>	import of >5kb
<i>ingA1</i>	<i>ingA2</i>	
<i>iga2</i>	<i>iga3</i>	import of >2kb

Microevolution of subgroup III

- 471 isolates of subgroup III, including strains from Mongolia (1994-95) and Moscow (1969-77 and 1994-97).
- 6 genetic markers: *opaB*, *opaD*, *iga*, *pgm*, *tbpB*, *IS1106*.
 - *pgm* distinguished ST5 (*pgm3*) from ST7 (*pgm19*)
 - *tbpB* (29 RFLPs)
 - *IS1106A* (10 RFLPs)
- Ancestral type reconstructed by comparison with other serogroup A subgroups.
- 8 genoclouds = groups of related variants in these 6 markers



Conclusions

- Introduction of novel virulent clones into a population may result in an epidemic wave.
- Clones identified as the source of epidemic disease in one country are likely to be found associated with increase incidence elsewhere soon after.
- Meningococcal populations are quite adaptable. A new clone (especially in serogroup B and C) may be able to fine tune its antigenic structure to the environment.
- However, not all the microevolution is a response to selection pressure; especially in serogroup A, serial population bottlenecks may result in the genetic diversity observed.

ANNEX 3.3

Characteristics of different strains and factors contributing to their virulence

by David Stephens, MD

David S. Stephens, MD

WHO CONSULTATION
W-135
Sept. 17-18, 2001

Pathogenesis of Invasive Meningococcal Disease

- Virulence of *Neisseria meningitidis*
- Human Transmission and Acquisition
- Human Susceptibility

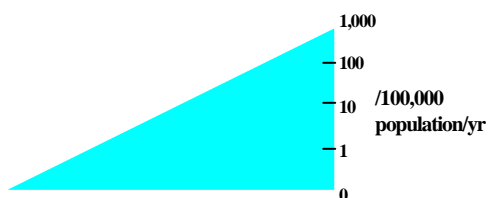
Biology of *Neisseria meningitidis*

- Pathogen exclusively of humans
- Genetic recombination and Genome plasticity
- Pathogen emergence and evolution

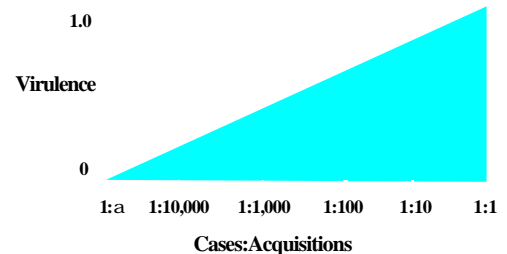
Classification of *Neisseria meningitidis*

- Serologic typing
 - Capsule (serogroup)
 - Major outer membrane protein (serotype)
 - Other outer membrane protein (serosubtype)
 - Lipooligosaccharide (immunotype)
 - B:2b:P1.5:L3,7,9
- Genomic typing
 - Multilocus enzyme electrophoresis (ET)
 - Multilocus sequence typing
 - ET-37 complex, ET-5

Incidence of Meningococcal Disease

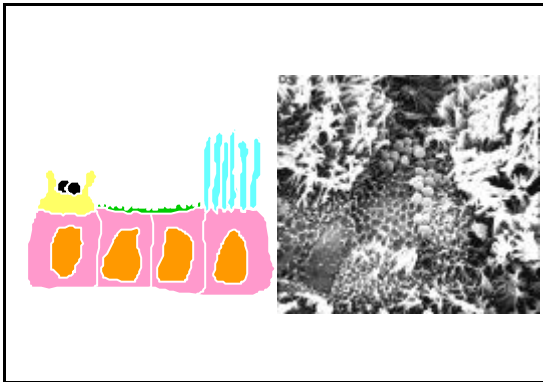
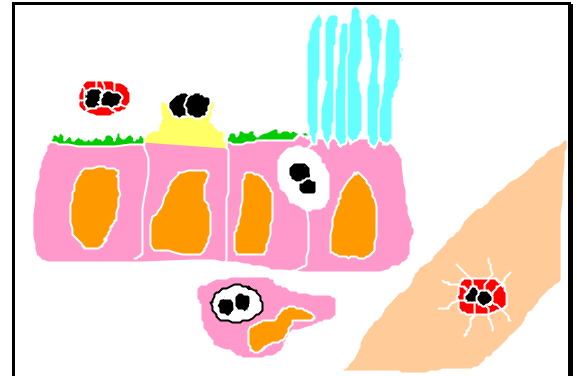


Virulence of *Neisseria meningitidis*



Virulent Meningococcal Clonal Groups

- Most epidemic and sporadic cases caused by a limited number of encapsulated clonal groups (ET-37, ET-5, A4 cluster)

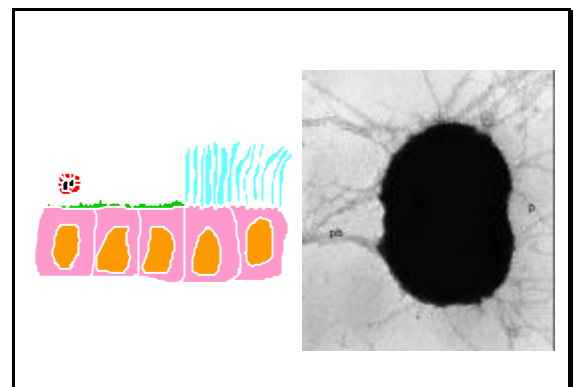


Meningococcal Iron-Acquiring Proteins

- | | |
|------------|--------------------------------|
| • HmbR | Hemoglobin |
| • TbpA & B | Transferrin |
| • LbpA & B | Lactoferrin |
| • HpuA & B | Hemoglobin-haptoglobin complex |

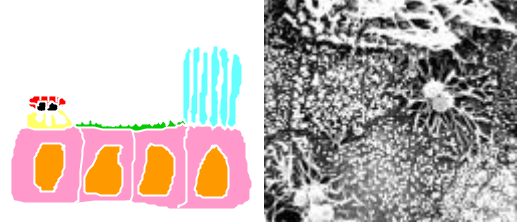
Meningococcal Outer Membrane

- Capsular polysaccharides, 13 serogroups
- Pili and other outer membrane proteins
- Lipopoly(oligo)saccharide (endotoxin)



Outer Membrane Proteins

- Porins: PorA (Class I) and PorB (Class 2 or 3)
- Class 4 (ompA homologue)
- Opa
- Opc
- Iron-acquiring proteins



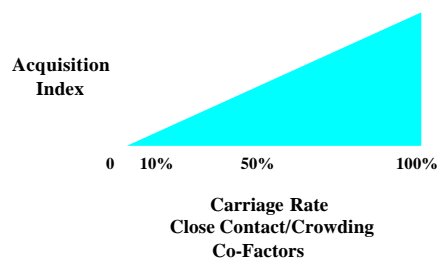
Meningococcal Genome

- ~2,200 kb (~51% G+C)
- Numerous repetitive elements and polymorphic regions
- Frequent recombination events
- FAM18 serogroup C sequence
- Z2491 serogroup A sequence
- MC58 serogroup B sequence

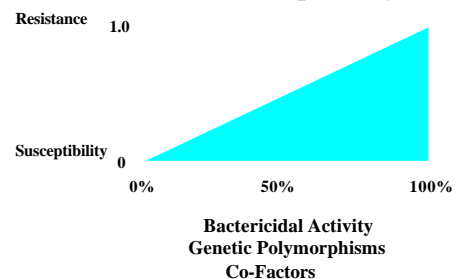
Meningococcal Virulence Mechanisms

- High frequency phase variation
- Structural (antigenic) variation
- Molecular mimicry
- Virulence islands

Human Transmission and Acquisition

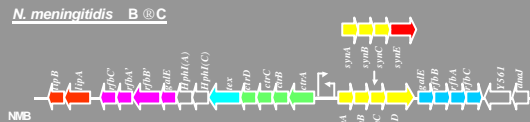


Human Susceptibility



[Replacement of capsular serogroups]

Capsule Switching – Gene Conversion of the Capsule Polymerase by Transformation



Other Data for Capsular Change *in Vivo*

- Meningococcal strain collections contain isolates with otherwise identical genetic markers (e.g., ET-type) that express different capsular polysaccharides.
- Meningococcal disease caused by B and C clonal strains with identical serotypes and ET types in the Czech Republic and Canada
- Emergence of ET-37 W-135 *N. meningitidis* outbreaks associated with the Hajj in 2000 and 2001.

Capsule and Virulence

- Capsule and specifically A,B,C,W-135,Y capsules requirement for almost all invasive meningococcal disease
- Thus far only capsular groups A, B, & C associated with large epidemic outbreaks (however recent emergence of Y, W-135, ?X indicate need for continued and enhanced surveillance)

Acknowledgements


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 - N. Rosenstein
 - A. Schuchat
 - J. Wenger
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 - R. Carlson (UGA)
 - Z. McGee (U. of Utah)
 - W. Zollinger (WRAIR)

ANNEX 3.4

Outbreak in the United Kingdom in 2001

by Mary Ramsay


(Public Health Laboratory Service (PHLS))



Meningococcal infection and the Hajj 2000-2001 England and Wales

Mary Ramsay, Susan Hahne
Steve Gray, Andrew Fox, Ed Kaczmarski

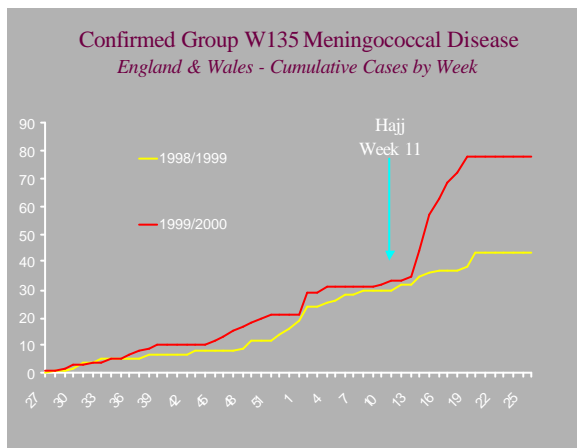
PHLS MEDICAL ILLUSTRATION
JULY 14.9




Mid March 2000

- PHLS Meningococcal reference unit detected increased number of cases W135 infection
 - many in people returning from the Hajj
- Case finding in UK
 - follow up of all W135 isolates PCR
 - EpiNet to CDCs and PHLS CDR front page
- International case findings

PHLS MEDICAL ILLUSTRATION
JULY 14.9

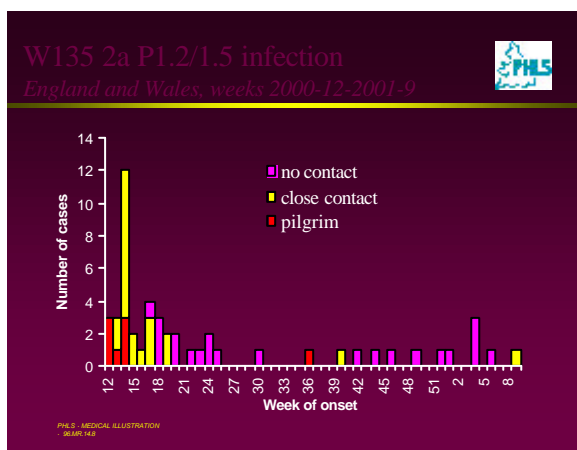





Meningococcal infection associated with the Hajj

- Total of 51 of confirmed W135 of the outbreak strain up to start of Hajj 2001
 - 8 in pilgrims / 22 in close contacts of pilgrims
 - 21 no history of contact
- One case of confirmed group A infection in a pilgrim
- An additional 17 cases confirmed W135 by PCR

PHLS MEDICAL ILLUSTRATION
JULY 14.9





Hajj 2000

- Following epidemic of group A meningococcal infection at Hajj 1987
 - Saudi visa requirements to have AC polysaccharide vaccine
- Approximately 19,749 people had UK visas for Hajj 2000

PHLS MEDICAL ILLUSTRATION
JULY 14.9

W135 infection



- 51 isolates all serotyped as 2a P1.5,2
 - eight fatalities - CFR 16%
- serotype/subtype associated with hyper-virulent, hyper-transmissible strains
 - ET-37 complex
 - more commonly seen as a group C organism in UK multi-centre

PHLS MEDICAL ILLUSTRATION
JGAR/148

Concerns about this outbreak



- not prevented by AC vaccination
- quadrivalent vaccine not routinely available in UK
- transmission maintained for four months after introduction
 - unlike previous group A introductions spread to wider Muslim community

PHLS MEDICAL ILLUSTRATION
JGAR/148

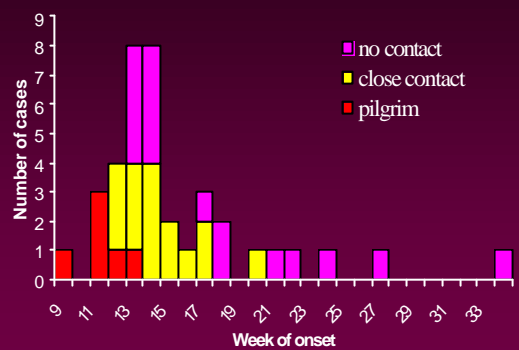
Carriage studies in Muslim population



- One centre swabbed (Gloucester)
 - 66 men attending Mosque
 - 2 carriers of outbreak strain
 - 1 carried group A, 2 carried group B

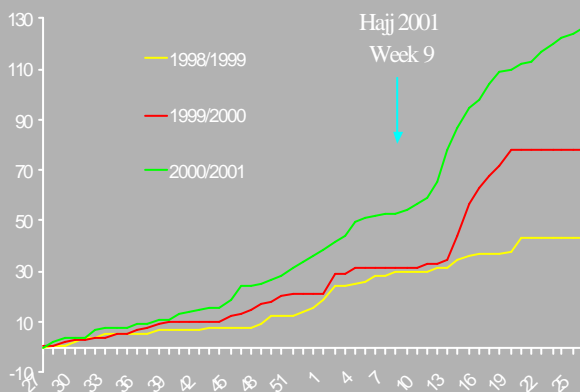
PHLS MEDICAL ILLUSTRATION
JGAR/148

W135 2a P1.2/1.5 infection England and Wales, weeks 9-34, 2001



PHLS MEDICAL ILLUSTRATION
JGAR/148

Confirmed Group W135 Meningococcal Disease England & Wales - Cumulative Cases by Week



W135 cases associated with the Hajj 2000 & 2001



- Outbreak of meningitis caused by organisms of strain W135 : 2a : P1.5,2 ST-11, in pilgrims returning from the Hajj.
- Between April 2000 – March 2001 ten non-culture (PCR) confirmed W135 cases were reported.
- *crA* C_{t} values for these ten samples ranged from C_{t} 22 – C_{t} 35. With four samples having C_{t} values greater than 34.

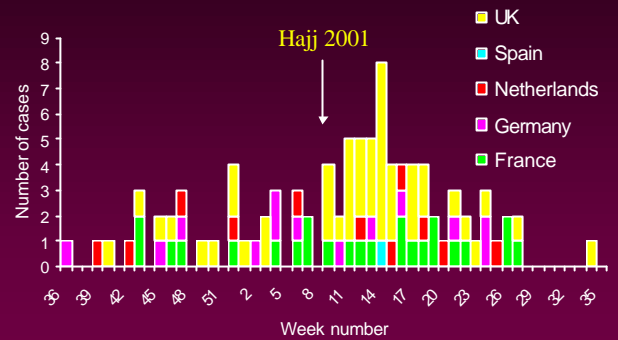
Source: PHLS, Public Health Laboratory Service

PHLS MEDICAL ILLUSTRATION
JGAR/148

MLST Classification of *ctrA* Positive W135 Cases

Patient	Date of Sample Collected	sero-Group	Sequence type	MLST Targets							MLST Classification
				<i>dhx2</i>	<i>adh</i>	<i>dhx1</i>	<i>dhx2</i>	<i>dhx3</i>	<i>dhx4</i>	<i>dhx5</i>	
1	02/04/2000	W135	NT	2	3	4	3	8	4	6	ST-11 (ST-11 complex)
2	06/04/2000	W135	P1.5, 2	2	3	4	3	8	4	6	ST-11 (ST-11 complex)
3	11/04/2000	W135	NT	2	3	4	3	8	4	6	ST-11 (ST-11 complex)
4	12/07/2000	W135	P1:18-1, 3	11	5	18	8	11	24	21	ST-22 (ST-22 complex)
5	14/07/2000	W135	P1:18-1, 3	11	5	18	8	11	4	21	ST-184 (ST-22 complex)
6	18/08/2000	W135	P1:18-1, 3	11	5	18	8	129	24	21	ST-1101 (ST-22 complex)
7	26/10/2000	W135	NT	2	3	4	3	8	4	6	ST-11 (ST-11 complex)
8	27/10/2000	W135	P1.5	2	3	4	3	8	4	6	ST-11 (ST-11 complex)
9	14/03/2001	W135	P1.5, 2	2	3	4	3	8	4	6	ST-11 (ST-11 complex)
10	21/03/2001	W135	P1.5, 2	2	3	4	3	8	4	6	ST-11 (ST-11 complex)

Sentinel surveillance of W135 2a P1.5,2 European Union, Sept 2000-date



PHLS - MEDICAL ILLUSTRATION
- SEMAR 14.8

ANNEX 3.5

Outbreak in Europe in 2001

by Anne Perrocheau

(WHO Consultant)

International outbreak of W135 meningococcal disease linked to Hajj 2000

A. Perrocheau¹, C. Meffre^{2,3}, J.F. Aguilera^{4,5}, S. Hahne^{2,5}

1 InVS, Saint Maurice, France
2 EPIET Program, Saint Maurice, France
3 RIVM, Bilthoven, The Netherlands
4 PHLS, CDSC, London, UK
5 PHLS, CDSC, Cardiff, UK

On behalf of :
The European investigation
team of the W135
meningococcal outbreak



History of meningococcal outbreaks linked to the Hajj

Year	Number of cases	<i>N. meningitidis</i> serogroup, clonal complex	Measures
1987	1841	A, III-1	AC vaccination for Hajj pilgrims
1992	182	A, III-1	Mecca population vaccination + AC vaccination for all pilgrims
2000	400	W135, ET-37 (+ A)	Mandatory ACYW135 vaccination for pilgrims in 2002

Background

- In the beginning of April : NRCs in the UK and France alerted about an increasing number of isolates of *N. meningitidis* serogroup W135, rare serogroup in France and UK
- The strain belonged to the ET 37 clonal complex
- All isolates were collected from pilgrims or their close contacts
- The case fatality rate was high
- There was evidence for an international spread of the disease
- In France, the 8th April, MOH recommended Rifampicin for all pilgrims and their household contact

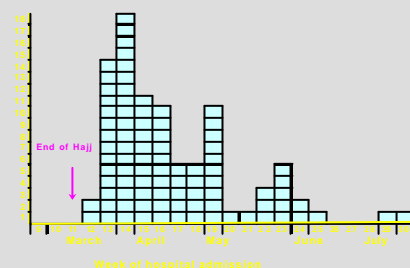
The European investigation team of the W135 meningococcal outbreak

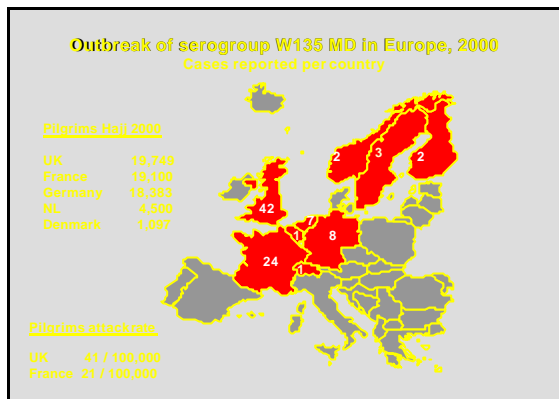
- Early in the course of the outbreak, representatives of MD surveillance in the most affected countries decided to conduct an international investigation
- Objectives
 - To describe the epidemiology of the outbreak in Europe
 - To evaluate the impact of the French response to the outbreak

Methods

- Case definition**
 - Patients with date of admission at hospital between 18 March and 31 July 2000
- Confirmed case**
invasive disease caused by *N. meningitidis* serogroup W135 with antigenic formula 2a: P1,2-P1,5 or belonging to the ET-37 clonal complex
- Probable case**
Pilgrim or contact of pilgrim with invasive disease, either with *N. meningitidis* W135 (PCR, specific Ag) or without laboratory confirmation

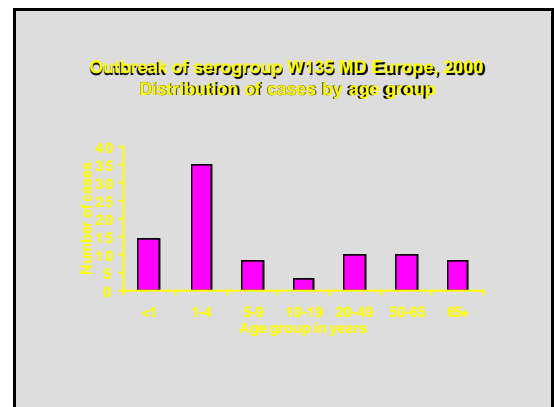
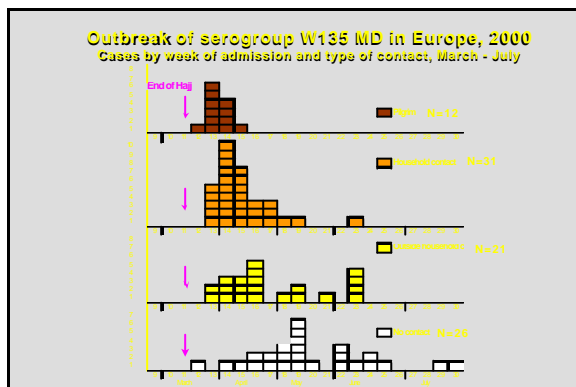
Outbreak of serogroup W135 MD in Europe, 2000
Cases reported by week of admission, March - July 2000, n=90





Méthodes

- ◆ Definition of the type of contact
 - Pilgrim
 - Household contact of pilgrim
 - Contact of pilgrim not living in the same household
 - No identified contact
- ◆ Identification of cases
 - National reference centers
 - National surveillance for MD
- ◆ Data collection
 - Standardised questionnaire
 - Telephone or face to face interviews
- ◆ Analysis
 - Logistic regression



Outbreak of serogroup W135 MD Europe, 2000
Characteristics of the cases

- ◆ Sex ratio

Male / Female	0.9
---------------	-----
- ◆ Median age

Pilgrim	51 years
Non pilgrim	2 years
- ◆ Proportion of patients aged 20 and over

Week 12 to 15	41%
Week 16 to 30	18%

Outbreak of serogroup W135 MD, Europe, 2000
Case fatality ratio

- ◆ CFR all cases 15.6%
- ◆ CFR reported from France and the UK

W135 outbreak	18.2%
All serogroup cases 95-99	8.5%
- ◆ Comparison W135 outbreak versus endemic disease

Without adjustment for age	RR 2.1, p = 0.01
With adjustment for age	RR 1.7, p = 0.07

Outbreak of serogroup W135 meningococcal disease in Europe following Hajj, 2000
Characteristic of the disease

Clinical signs	n	%
Meningitis	29	43
Septicemia	23	34
Both (%)	15	22
Total	67	100
Purpura fulminans	12	18
Unusual clinical forms		
Arthritis	6	
Osteomyelitis	1	
Pneumonia	1	

Evaluation of the measures implemented in France

Methods

- ♦ Calculation of the ratio of the cases occurring after / before the 8th april, in France divided by the same ratio in UK

$$\frac{[\# \text{ of cases after 8 april} / \# \text{ of cases before 8 april}] \text{ in France}}{[\# \text{ of cases after 8 april} / \# \text{ of cases before 8 april}] \text{ in UK}}$$

- pilgrim and household contacts
- cases outside pilgrim household

- ♦ Comparison of the result to 1
 - < 1 : impact of the measure
 - > 1 : no impact of the measure

Outbreak of serogroup W135 meningococcal disease in Europe following Hajj, 2000
Evaluation of the response in France

Type of contact	UK Cases		France Cases		Ratio F(after/before) UK(after/before)	p
	Before	After	Before	After		
Pilgrim + HH contact	17	5	7	5	2.43	0.27
Non household contact	2	18	2	10	0.56	0.62

Discussion

- ♦ This is the first description of a serogroup W135 outbreak
- ♦ The initial large proportions of patients older than 20 years and of deaths were associated with pilgrim's characteristics
- ♦ The diffusion of the strain in the population was related to the type of contact with a pilgrim
- ♦ The evaluation of the French measures did not reveal a positive impact
- ♦ After Hajj 2001 new cases have been reported in several european countries

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